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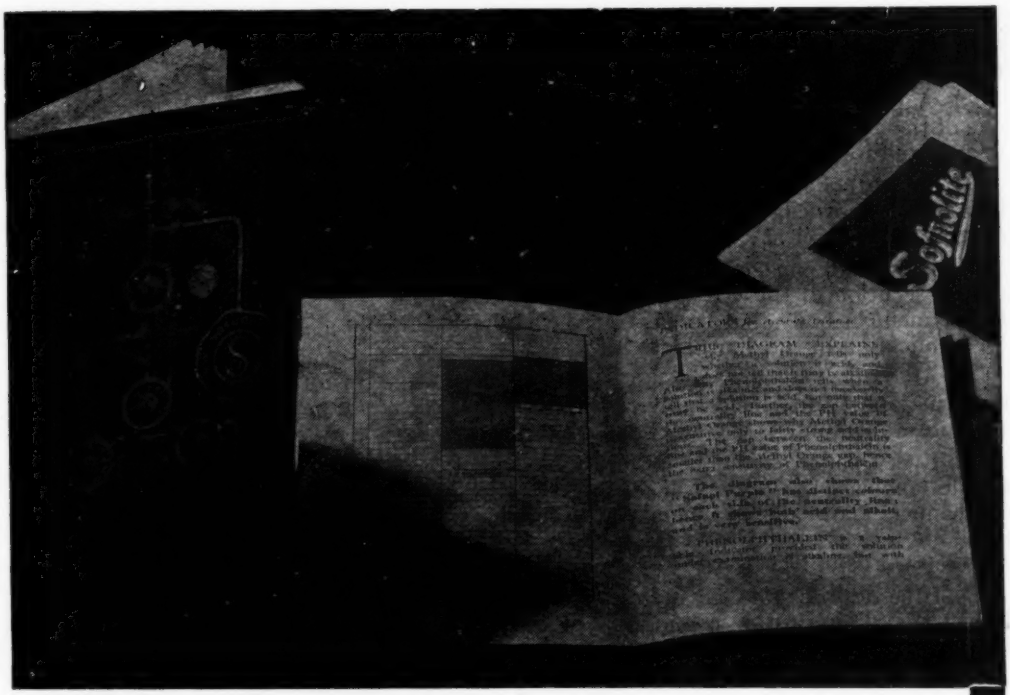

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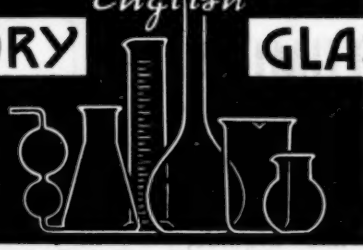

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By R. Culford Bell and Lindsay H. Briggs.

The alkaloid from the green fruit of *Solanum aviculare*, previously regarded as a distinct alkaloid " purapurine," has now been shown to be identical with solasonine.

The fruit from *Solanum aviculare* (Maori name " poro-poro ") has already been investigated by Levi (*J. Soc. Chem. Ind.*, 1930, **49**, 395 T), who isolated a glucosidic alkaloid, m. p. 220—230°, yielding a sugar-free base on hydrolysis. Both compounds were obtained only as green amorphous powders and, of a number of derivatives prepared from the glycoside, only the thiocyanate was obtained crystalline. Since both compounds appeared to possess properties different from those of known compounds in this series, he named these compounds purapurine and purapuridine respectively, probably under the mistaken impression that the Maori name for this plant was " pura-pura." On the basis of analysis, formulæ $C_{48}H_{73}O_{18}N_2$ and $C_{37}H_{57}O_6N_2$ were suggested for the glucosidic alkaloid and the free base respectively. Both formulæ contain odd valencies and are therefore incorrect. The difference between the formulæ is $C_{11}H_{16}O_{12}$, which by addition of OH should give the sugar produced on hydrolysis. Such a compound, $C_{11}H_{17}O_{13}$, also contains odd valencies and even if it were $C_{11}H_{16}O_{13}$ or $C_{11}H_{18}O_{13}$ it still does not represent a normal carbohydrate.

The green berries of the shrub have now been reinvestigated. By working up the extract obtained by means of hot alcohol, a colourless crystalline alkaloid, m. p. 284—285° (decomp.), has been obtained in good yield; this is hydrolysed by 3% hydrochloric acid to the free base, m. p. 197·5—198·5°. From both the glycoside and the free base a number of crystalline salts have been prepared. The melting points of all these compounds agree with those of solanine-s and its corresponding free base, solanidine-s (now named solasonine and solasodine respectively; see following paper), from *S. sodomæum*.

To make a more complete comparison, authentic solasonine has been extracted from the green berries of *S. sodomæum*, and the same series of derivatives prepared from the pure alkaloid. In order to avoid differences in the melting and especially the decomposition points of such compounds due to different rates of heating (cf. Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404) the melting points of both sets of compounds and their mixtures have been observed simultaneously in the same melting point apparatus (electrically heated copper block). The melting points are set out in the following table.

Derivative.	Alkaloid from *S. aviculare*, m. p.	Solasonine, m. p.	Mixed m. p.
Glucoside	276—277°	275—276°	275—276°
Picrate	200·5—201	199—199·5	200—200·5
Picrolonate	231	230	230
Free base	197·5—198·5	197·5—198·5	197·5—198·5
Picrate	144	143·5	144—144·5
Picrolonate	234	233	234
Hydrochloride	314	312	312·5
Hydriodide	293	291	291·5
Tartrate	222	222	221
Oxalate	248	249	248

(All the above compounds melt with decomposition except the free bases.)

It is possible in the *Solanum* alkaloids that the same base can be united to different sugars, giving rise to different glycosidic alkaloids. The melting points, however, of the glycosides and their salts, previously unprepared, as well as the mixed melting points, indicate that both the glycosides and the free bases are identical. It is therefore not necessary to go to the more laborious procedure of identifying the glycoside through the sugars produced on hydrolysis (see Part IV; this vol., p. 17).

Further, crystal measurements of the hydrochloride of the free base are also in complete agreement with those of an authentic specimen. There can be no doubt, therefore, that the alkaloid from *S. aviculare* is identical with solasonine in all respects. The use of the names " purapurine " and " purapuridine " for these compounds should therefore be discontinued.

Solasonine has also been identified from the fruit of *S. xanthocarpum* (Saiyed and Kanga, *Proc. Indian Acad. Sci.*, 1936, **4**, *A*, 255; Gupta and Dutt, *J. Indian Chem. Soc.*, 1938, **15**, 95; cf. Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404, 2467) and Anderson and Briggs (J., 1937, 1036) have reported its occurrence in the green berries of *S. auriculatum* (see Part III, this vol., p. 12, for further observations on the alkaloids from this source).

As already reported (Briggs, *Nature*, 1939, **144**, 247), analytical data now agree with formulæ $C_{45}H_{73}O_{16}N$ and $C_{27}H_{43}O_2N$ for solasonine and solasodine respectively. These formulæ have been confirmed by the analyses of a number of derivatives (see Part II) and also by Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329). Solasonine and solasodine crystallise with four and one molecule of water of crystallisation respectively and in both cases this is only removed with considerable difficulty.

Experimental.

Isolation of Solasonine.—The dried green berries from shrubs growing in Auckland were exhaustively extracted with alcohol in the apparatus described by Briggs (*Ind. Eng. Chem.*, [*Anal.*], 1937, **9**, 250). When most of the alcohol had been removed from the extract by distillation, excess of 2% aqueous acetic acid was added, and the residual alcohol removed by steam-distillation. The aqueous solution was filtered, the filtrate boiled, and the crude solasonine precipitated in a granular form by the addition of ammonia (precipitation in the cold produces a jelly). The crude alkaloid was purified by solution in dilute acetic acid and reprecipitation with ammonia, followed by repeated crystallisation from 60—80% alcohol and 80% dioxan–water (crystallisation from higher concentrations of alcohol or dioxan produces a jelly) to give colourless pointed plates, m. p. 284—285° (decomp.), $[\alpha]_D^{25°}$ − 68·7° in alcohol (l = 2 dcm., c = 0·2320) (Found: C, 60·5; H, 8·4; N, 1·6. Calc. for $C_{45}H_{73}O_{16}N,\frac{1}{2}H_2O$: C, 60·6; H, 8·4; N, 1·6%).

The alkaloid from the green berries of *S. sodomæum* growing in Auckland was similarly extracted and purified; $[\alpha]_D^{25°}$ − 53·0° in alcohol (l = 2 dcm., c = 0·2736) (Found: C, 60·5; H, 8·4; N, 1·6%).

Both compounds gave with concentrated sulphuric acid in the cold an amber-red colour and with concentrated nitric acid a brownish-yellow colour (for further colour reactions, see the following paper).

The picrate and the picrolonate were obtained by mixing the two components in hot alcoholic solution and were twice recrystallised from 60% alcohol.

Hydrolysis of Solasonine.—The pure alkaloid was heated with excess of 3% hydrochloric acid at 100° for 3 hours. (Solasodine hydrochloride, in contrast to solasonine hydrochloride, is only slightly soluble in the cold and is precipitated in a crystalline condition even from the hot solution.) After cooling, the hydrochloride was collected, recrystallised twice from 80% alcohol, suspended in hot water, basified with ammonia, and heated at 100° for ½ hour. The solasodine was collected after cooling and repeatedly crystallised from 80% alcohol, forming hexagonal plates, m. p. 197·5—198·5°, $[\alpha]_D^{25°}$ − 97·1° in methyl alcohol (l = 1 dcm., c = 0·1400) (Found: C, 77·7, 77·7; H, 10·5, 10·6; N, 3·8. Calc. for $C_{27}H_{43}O_2N$: C, 78·45; H, 10·4; N, 3·4%). The hydrochloride had $[\alpha]_D^{24°}$ − 68·0° in methyl alcohol (l = 1 dcm., c = 0·4708).

In the same manner solasodine was obtained by the hydrolysis of solasonine from *S. sodomæum*; $[\alpha]_D^{26°}$ −80·4° in methyl alcohol (l = 1 dcm., c = 0·1984) (Found: C, 77·9, 77·9; H, 10·5, 10·7; N, 3·4, 3·5%).

The colour reactions of both compounds are the same as those of the glycosides.

The salts of both compounds were prepared by addition of the components in hot alcohol and recrystallised in all cases from 80% alcohol. The melting points and mixed melting points are recorded on p. 1.

The hydrochlorides of solasodine from *S. aviculare* and *S. sodomæum* have been examined by Dr. F. J. Turner, Otago University, to whom we are indebted for the following report. (The crystals are too fragile for the crystal angles to be measured, but the optic axes have been measured.)

" Solasodine hydrochloride (*ex S. aviculare*):

$2V$ (the optic axial angle) = 80°, 82°, 82°, 84°, mean 82° ± 2°.

Optical character positive.

Some crystals are elongated parallel to β with γ nearly perpendicular to the plane of flattening. These have the same axial angle and the shape is due to variation in habit.

Solasodine hydrochloride (*ex S. sodomæum*):

$2V$ = 80°, 82°, 86°, 90°, mean 85° ± 5°.

Optical character positive.

Also, one measurement, $2V$ = 88°, optical character negative.

The hydrochlorides appear to be identical as regards habit, orientation and optic axial angle."

The analyses are by Dr.-Ing. A. Schoeller.

We are indebted to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for grants, and one of us (R. C. B.) for a Sir George Grey Scholarship.

Auckland University College, Auckland, New Zealand. [*Received, January 30th*, 1941.]

2. Solanum *Alkaloids. Part II. Solasonine.*

By Lindsay H. Briggs, Robert P. Newbold, and Norman E. Stace.

Further analyses now support formulæ $C_{45}H_{73}O_{16}N$ and $C_{27}H_{43}O_2N$ for the glycosidic alkaloid solasonine (*ex S. sodomæum*) and its free base solasodine, respectively. The difference between the glycoside and the free base leads to the formulation of solasonine analogously to solanine by the union of the trisaccharide containing rhamnose, galactose, and glucose units with one molecule of solasodine and not two as suggested by Oddo. Solasodine now differs from solanidine only by an extra oxygen atom and, like it, contains the steroid nucleus and resembles most other steroids in possessing one hydroxyl group in a *cis*-position at C_3 and a double bond at C_5–C_6. It forms a monoacetyl derivative soluble in acids, *dihydrosolasodine* on catalytic hydrogenation with palladised charcoal, and adds on two bromine atoms in acetic acid solution. Dehydration with alcoholic hydrogen chloride yields $\Delta^{3:5}$-solasodiene with an ultra-violet absorption spectra characteristic of double bonds in different rings. The nitrogen is not tertiary as previously suggested, but combined with the second oxygen atom or the related carbinol-amine as a quaternary hydroxide. The action of nitrous acid yields a quaternary *nitrite*, which is an anhydro-salt identical with the so-called azosolasodine of Oddo. Methyl and ethyl iodide both react, forming the hydriodide in both cases and not the methiodide and ethiodide as suggested previously. Hydrogenation of solasodine and solasodiene with a platinum oxide catalyst yields tetrahydrosolasodine (dihydro*chano*solasodanol) and *hexahydrosolasodiene* (*dihydro*chano*solasodan*) respectively by saturation of the normal double bonds and further, it is suggested, by opening up of the heterocyclic rings. A full formula for solasonine embodying these results is proposed.

From the green fruit of *Solanum sodomæum* ("Dead Sea Apple") a glycosidic alkaloid has been isolated by Oddo and Colombano (*Gazzetta*, 1905, **35**, i, 27), Romeo (*ibid.*, 1905, **35**, ii, 579), and Soldaini (*Boll. Chim. Farm.*, 1905, **44**, 769, 808, 843), which is hydrolysed by dilute acids to a mixture of sugars and a basic aglycone. Both the glycosidic base and the free base differed from the corresponding compounds, solanine and solanidine respectively, obtained from *S. tuberosum* (potato) and other *Solanum* species by various workers (cf. Henry, "The Plant Alkaloids," 1939, p. 642) and to differentiate them Oddo proposed the names solanine-s for the glycosidic base and solanidine-s for the free base. To avoid this awkward nomenclature, Rochelmeyer (*Arch. Pharm.*, 1937, **275**, 336) has renamed these compounds solasonine and solasodine respectively.*

Over a period of thirty years papers by Oddo and co-workers on the constitution of solasonine have appeared (Oddo and Caronna, *Ber.*, 1936, **69**, 283, and earlier papers) based on the formulæ $C_{54}H_{96}O_{18}N_2,H_2O$ for the glycosidic base and $C_{18}H_{31}ON$ for the aglycone, solasodine. Recent analyses (Briggs, *Nature*, 1939, **144**, 247) support formulæ $C_{45}H_{73}O_{16}N$ and $C_{27}H_{43}O_2N$ for solasonine and solasodine respectively, confirmed in the latter case by Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329). The discrepancy between the present formulæ and those suggested by Oddo places a different interpretation on the experimental work of the latter.

In the first place, Oddo found that glucose, galactose, and rhamnose, besides solasodine, were produced by the hydrolysis of solasonine. From the molecular formulæ of the two bases he concluded that these three sugars were combined together with two molecules of solasodine, thus:

$C_{18}H_{30}ON$	$-C_6H_{12}O_5$	$-O-C_6H_{12}O_5$	$-O-C_6H_{12}O_4$	$-O-C_{18}H_{30}N,H_2O$ ($C_{54}H_{96}O_{18}N,H_2O$)
solasodine	glucose	galactose	rhamnose	solasodine

Since the formula $C_{45}H_{73}O_{16}N$ now proposed for solasonine differs from that of solasodine, $C_{27}H_{43}O_2N$, by 18 carbon atoms, it is clear that solasonine is built up analogously to solanine from these three sugars and only one molecule of solasodine, thus:

$C_6H_{11}O_4-O-$	$C_6H_{10}O_4$	$-O-C_6H_{10}O_4$	$-O-C_{27}H_{42}ON$ ($C_{45}H_{73}O_{16}N$)
rhamnose	galactose	glucose	solasodine

The order of the three sugars is based partly on Oddo's work and on analogy with the order of the sugars in solanine (Zemplén and Gerecs, *Ber.*, 1928, **61**, 2294; Oddo and Caronna, *ibid.*, 1934, **67**, 446). Solasonine does not react with phenylhydrazine or with hydroxylamine, so it would appear that all the

* Oddo also referred to the bases solanine and solanidine from *S. tuberosum* as solanine-t and solanidine-t, but Rochelmeyer (*loc. cit.*) has suggested altering these names to solatunine and solatubine, respectively, indicative of their origin. We agree with Henry (*op. cit.*) that this alteration is both confusing and unnecessary—the simplest procedure being to eliminate the suffix t. Other workers had already introduced a satisfactory nomenclature for the degradation products of solanidine (cf. Soltys and Wallenfels, *Ber.*, 1936, **69**, 811) based on the normal steroid nomenclature.

sugar molecules are united through their potential aldehyde structures. To the authors' knowledge the trisaccharide forming the glycosidic moiety of solasonine does not occur elsewhere in the plant kingdom other than in the *Solanum* genus.

It may be suggested in passing that, since solasodine differs from solanidine only by an additional oxygen atom and since also solasonine and solanine are similarly built up from the same sugars, the older formula for solanine should be replaced by $C_{45}H_{73}O_{15}N$ of the partial structure

$$\underset{\text{rhamnose}}{C_6H_{11}O_4} \quad -O-\underset{\text{galactose}}{C_6H_{10}O_4} \quad -O-\underset{\text{glucose}}{C_6H_{10}O_4} \quad -O-\underset{\text{solanidine}}{C_{27}H_{42}N\ (C_{45}H_{73}O_{15}N)}$$

The formula $C_{27}H_{43}O_2N$ now proposed for solasodine is supported by analyses of the free base, its salts and a number of derivatives. Solasodine gives analytical figures agreeing with the formula $C_{27}H_{45}O_3N$ when normally dried for combustion, but with $C_{27}H_{43}O_2N$ when more vigorously dried. This water of crystallisation is only lost with difficulty from solasodine and most of its derivatives. On biochemical grounds a compound containing 27 carbon atoms is also to be preferred to the formula $C_{26}H_{43}O_3N$ originally suggested (Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404, 2467; cf. Saiyed and Kanga, *Proc. Indian Acad. Sci.*, 1936, **4**, *A*, 255), since there are no well-authenticated steroid derivatives containing 26 carbon atoms with the exception of the bases solanocapsine and solanocapsidine (Barger and Fraenkel-Conrat, J., 1936, 1537), to which the same argument also probably applies.

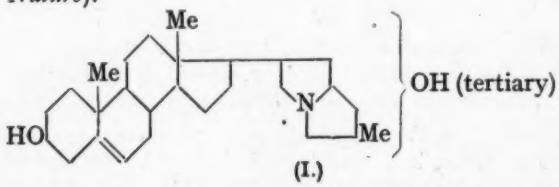
On selenium dehydrogenation, solasodine yields pyrrole bases and methyl*cyclo*pentenophenanthrene, thus indicating its steroid structure (Rochelmeyer, *Arch. Pharm.*, 1936, **274**, 543).

According to Oddo solasodine contains two active hydrogen atoms (Zerewitinoff determination) and forms an amorphous diacetyl derivative. Since it gave by the action of nitrous acid a compound "azosolasodine" containing a further nitrogen atom, Oddo concluded, on the basis of the formula $C_{18}H_{31}ON$, that solasodine contains both a hydroxyl and a secondary amino-group. We have confirmed the fact that completely dry solasodine contains two active hydrogen atoms. We have also prepared "azosolasodine" of the same melting point, but find that, when this is treated with dilute aqueous or alcoholic ammonia, solasodine is regenerated, thus indicating the salt-like character of "azosolasodine." This at first suggested that the nitrogen is tertiary, which was apparently confirmed by the facile action of methyl and ethyl iodide to yield quaternary salts, m. p. 286° (decomp.) and 284° (decomp.), respectively. Moreover, Simon's reaction (*Compt. rend.*, 1897, **125**, 536) for secondary amines is negative with solasodine (and also solasoline). A Herzig–Meyer estimation indicates the absence of a methylimino-group (and incidentally methoxy- and ethoxy-groups) and, since no alkyl groups other than methyl are known to be attached to tertiary nitrogen atoms in naturally occurring alkaloids, it is concluded that the nitrogen forms part of two rings.

To explain the presence of two active hydrogen atoms in solasodine, both oxygen atoms must be present as hydroxyl groups. A carbonyl group is excluded by the fact that solasodine may be recovered by decomposition of the Grignard compound in the Zerewitinoff estimation. Solasodine forms a monoacetyl derivative, m. p. 195° (Briggs, *Nature*, 1939, **144**, 247; Rochelmeyer, *Arch. Pharm.*, 1939, **277**, 329), which is readily soluble in dilute acids, thus confirming the presence of one hydroxyl group. Solasodine gives a precipitate with digitonin (Rochelmeyer, *Arch. Pharm.*, 1937, **275**, 336, and present work), whereas the acetyl compound does not. This places the hydroxyl which can be acetylated in position 3 in the *cis*-position to the methyl group on C_{10}. It was suggested by one of us that the remaining hydroxyl group, since it is not acetylated, is probably tertiary.

Solasodine is unsaturated, forming a dihydro-derivative and a dibromo-derivative by addition (see later). It must therefore contain one double bond, provisionally placed, by analogy with other steroids, at C_5–C_6.

On the above evidence, and assuming a cholesterol carbon skeleton and one point of attachment of the basic structure to the homocyclic portion, the structure (I) was suggested by one of us (Briggs, *Nature*).



(I.)

Further evidence has now confirmed some of these conclusions, but modifications and corrections have also to be made.

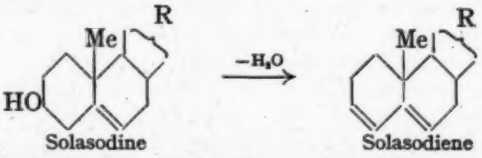
Hydrogenation of solasodine in acetic acid solution, a palladium–norite catalyst being used, yields *dihydrosolasodine*, $C_{27}H_{45}O_2N$, m. p. 209·5—211·5°. Acid conditions are necessary for the hydrogenation, as solasodine is not reduced in alcoholic solution, but is immediately reduced on the addition of cinnamic acid added to test the activity of the catalyst. The presence of one normal carbon-to-

carbon double bond is confirmed by the fact that addition of bromine in acetic acid solution ceases after the addition of two atoms.

Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329), using the more reactive platinum oxide catalyst, obtained a tetrahydrosolasodine, $C_{27}H_{47}O_2N$, m. p. 286—288·5°. We had already prepared the same compound of slightly higher melting point, by the same procedure. Since dihydrosolasodine does not give the ordinary tests for unsaturation with tetranitromethane, antimony trichloride or bromine, we regard this tetrahydro-derivative in the meantime as being formed by saturation of the ordinary double bond and ring fission of the heterocyclic rings (see below for further details).

Oddo and Cesaris have reported (*Gazzetta*, 1914, **44**, ii, 191) that the action of alcoholic hydrogen chloride on solasodine yields solasodine ether, $(C_{18}H_{30}N)_2O$, m. p. 176—177°, by loss of water between two molecules. We have now shown that methyl- or ethyl-alcoholic hydrogen chloride removes one molecule of water intramolecularly with the formation of solasodiene,* $C_{27}H_{41}ON$, m. p. 169·5—170·5°. The compound of higher melting point, 176—177°, was also isolated by Rochelmeyer (*Arch. Pharm.*, 1937, **275**, 336) by working up the mother-liquors in the purification of solasodine obtained by the acid hydrolysis of solasonine. He regarded this as a new alkaloid, solanosodine, but we prefer to regard it as a by-product in the hydrolysis, since we have also obtained the same product on working up the mother-liquors after the hydrolysis of pure solasonine [cf. also the formation of solanidiene (solanthrene) during the hydrolysis of solanine; Soltys and Wallenfels, *loc. cit.*]. The melting point of solasodiene obtained by other workers is higher than that of our product, probably owing to an impurity, since the melting point of our product was unchanged by repeated crystallisation from different solvents and traces of solasodine actually raised the melting point. That the hydroxyl group is lost from the C_3 atom during this process is shown by the fact that solasodiene no longer gives an insoluble digitonide.

The original double bond in solasodine was provisionally placed at C_5–C_6 by analogy with the majority of other steroid compounds, including the proof of this position of the double bond in solanidine by Rochelmeyer (*Ber.*, 1938, **71**, 226). This position has been confirmed by the following facts. That the double bonds are conjugated is indicated by a positive Rosenheim reaction (*Biochem. J.*, 1929, **23**, 47; cf. also Schoenheimer and Evans, *J. Biol. Chem.*, 1936, **114**, 567) and an immediate intense crimson coloration with antimony trichloride in chloroform solution. The ultra-violet absorption spectrum has been observed by Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329), who found a maximum at 2340 A., log ε 4·34; we also had measured the absorption spectrum, obtaining a slightly higher value at 2345 A., log ε 4·44. Both values are consistent with conjugated double bonds existing in separate rings, *i.e.*, in C_3–C_4 and C_5–C_6 positions.



Solasodine Solasodiene

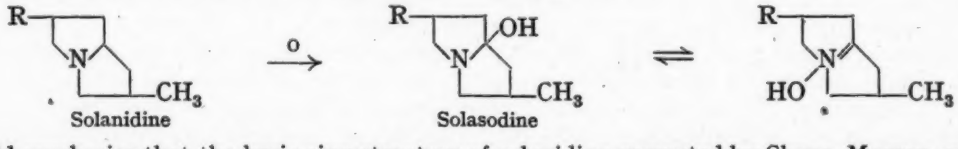
Such double bonds should have the *trans*-configuration and therefore would not be expected to add on maleic anhydride in the normal manner, a fact which we have confirmed experimentally. Also addition of bromine in acetic acid solution ceases after the addition of two atoms (see later). Velstra (*Nature*, 1939, **144**, 485) has shown that $\Delta^{3:5}$-cholestadiene with conjugated double bonds in separate rings also adds on only two atoms of bromine.

Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329) has found that oxidation of solasodine with Oppenauer's reagent yields a ketone, $C_{27}H_{41}O_2N$, m. p. 184—185°, which we regard as Δ^4-solasoden-3-one, the double bond shifting in the process to the αβ-position in relation to the carbonyl group, *i.e.*, to the C_4–C_5 position, as is usual in such oxidations in the steroid series. This compound no longer gives a precipitate with digitonin, thus indicating the oxidation of the C_3 hydroxyl to a carbonyl group. We have also obtained a compound, m. p. 186°, which is probably identical with Δ^4-solasoden-3-one, by oxidising solasodine with copper powder (cf. Diels, Gädke, and Körding, *Annalen*, 1927, **459**, 21, and a similar experiment on solanidine by Schöpf and Hermann, *Ber.*, 1933, **66**, 298; Rochelmeyer, *ibid.*, 1938, **71**, 226). This compound gives a positive test with Zimmermann's reagent (*Z. physiol. Chem.*, 1935, **233**, 257; 1936, **245**, 47; Kaziro and Shimada, *ibid.*, 1937, **249**, 220), thus confirming the presence of a carbonyl group at C_3.

It can thus be stated with some degree of certainty that one hydroxyl group of solasodine is at position 3 and the normal carbon-to-carbon double bond is at C_5–C_6.

* We suggest the name solasodan for the basic saturated but unsubstituted structure of solasodine, which on this nomenclature would become solasodenol but we prefer to retain the original name for the parent substance.

It was originally suggested that the second hydroxyl in solasodine was tertiary owing to the fact that only a monoacetyl derivative is formed. Various tests for tertiary alcohols were negative, *e.g.*, with Denigès's reagent (*Compt. rend.*, 1898, **126**, 1145, 1277), and a tertiary alcohol should be dehydrated at least as readily as the secondary alcoholic group at C_3 by the action of alcoholic hydrogen chloride (*loc. cit.*) or aluminium oxide at 250° (Rochelmeyer, *Arch. Pharm.*, 1939, **277**, 329), but in both cases the only product is solasodiene. It is now clear, however, that the second hydroxyl group is present combined with the nitrogen as a quaternary hydroxide or the related carbinol-amine and we suggest that the basic portion of solasodine may be formulated as follows, a possible mode of phytosynthesis being from mild oxidation of solanidine (cf. the formation of ψ-strychnine and ψ-brucine from the true bases; Leuchs, *Ber.*, 1937, **70**, 1543; Leuchs and Tessmar, *ibid.*, p. 2369):



Solanidine Solasodine

We would emphasise that the basic ring structure of solanidine suggested by Clemo, Morgan, and Raper (J., 1936, 1299) is the only structure possible, provided that two assumptions are made—that the carbon skeleton is the same as in cholesterol and that the basic ring structure has only one point of attachment to the steroid ring system. In the first case there is no exception in the whole of the steroid field to the fact that the carbon side chains of C_{27} sterols whose structures are known are all the same as in cholesterol. Further, the formation of Diels's hydrocarbon on selenium dehydrogenation of both solanidine (Soltys and Wallenfels, *Ber.*, 1936, **69**, 811) and solasodine (Rochelmeyer, *Arch. Pharm.*, 1936, **274**, 543) supports the second assumption. For these reasons we have included the same structure in solasodine.

In contrast with the berberine alkaloids and ψ-strychnine, solasodine appears to behave in many of its chemical reactions as the quaternary hydroxide rather than the related carbinolamine or ketone-amine. Solasodine is alkaline to litmus in alcoholic solution. The compound formed by the action of acetic acid and sodium nitrite on solasodine gives the analytical figures required for $C_{27}H_{42}O_3N_2$, indicating the loss of water in the process. We regard this compound, the " azosolasodine (azosolanidine-s) " of Oddo, as a quaternary *nitrite* rather than the nitrosoamine of the related ketone-amine, since treatment with dilute aqueous ammonia regenerates solasodine. The compound is not formed when hydrochloric acid replaces acetic acid in the preparation, solasodine hydrochloride being formed instead. Oddo and Caronna had also observed (*Ber.*, 1936, **69**, 283) that reduction of " azosolasodine " with zinc and acetic acid, followed by treatment with alkali, regenerates solasodine. In this case it is suggested that the main action is concerned not with the reducing agent but with the alkali treatment.

It has now been shown that the facile action of methyl iodide and ethyl iodide on solasodine does not yield the methiodide and ethiodide respectively, but in both cases forms solasodine hydriodide. The product from both these reactions has the same melting point as the hydriodide, the melting point of which is not depressed on admixture. It must be noted, however, that depression of melting point must be interpreted with caution in this series where the salts melt with decomposition and it has been observed that a mixture of the hydrobromide, m. p. 309·5° (decomp.), with the hydrochloride, m. p. 316·5—317·5° (decomp.), has m. p. 314—314·5° (decomp.). However, treatment of the products formed by the action of methyl iodide and ethyl iodide on solasodine with dilute aqueous ammonia regenerates solasodine. The action of methyl iodide to give the hydriodide is more simply explained through the quaternary hydroxide, *i.e.*, $\geqslant N\cdot OH + CH_3I \longrightarrow \geqslant NI + CH_3\cdot OH$, rather than the carbinol-amine, which would be expected to give an *N*-methylated product as in the action of methyl iodide on ψ-strychnine (Blount and Robinson, J., 1932, 2305; Leuchs, *Ber.*, 1937, **70**, 2455).

A further reaction of solasodine as the quaternary hydroxide is afforded by the results of bromination. In chloroform solution, exactly three atoms of bromine per mole of solasodine are required before decoloration ceases, and in acetic acid solution decoloration ceases when two atoms of bromine have been added. In the first case, two atoms of bromine are utilised in addition to the normal double bond and the extra atom of bromine is possibly acquired by reaction of the quaternary hydroxide to form the quaternary bromide and hypobromite: $2\ \geqslant N\cdot OH + Br_2 \longrightarrow \geqslant NBr + \geqslant N\cdot OBr + H_2O$. In the second case the quaternary hydroxide is first converted into the acetate and this portion of the molecule no longer reacts with bromine (cf. bromination of diketonucidine, and its perchlorate; Holmes and Robinson, J., 1936, 603). The products from both methods of bromination could not be crystallised satisfactorily from non-aqueous solvents, but when crystallised from a mixture of water, acetone, and alcohol containing a little hydrobromic acid, both formed the same *hydrobromide* (needles), m. p. 303°

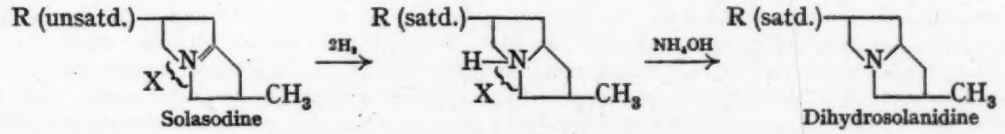
(decomp.), undepressed on admixture. Analysis, however, indicated the loss of one atom of bromine, probably by hydrolysis during the crystallisation (cf. cholesterol dibromide; Lifschütz, *Z. physiol. Chem.*, 1919, **106**, 271).

Similarly, bromination of solasodiene in chloroform solution required three atoms before decoloration ceased, and in acetic acid solution absorption of bromine ceased after the addition of two atoms. The product from the first reaction was isolated as a colourless hydrobromide, m. p. 205—209°, which, however, rapidly darkened in air and was not analysed. Further experiments on this phase are in hand.

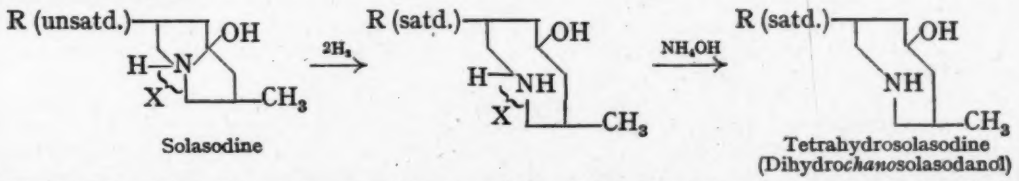
In an attempt to replace both hydroxyl groups by chlorine atoms, to produce a dichloro-derivative which on reduction might possibly give solanidene under the previous formulation, the action of thionyl chloride on solasodine in pyridine solution was investigated. Although all the reactants were thoroughly dried, solasodine hydrochloride formed immediately when they were mixed in the cold—a result which is more readily explained by means of the quaternary hydroxide form.

The existence of solasodine as a stable quaternary hydroxide rather than the related carbinol-amine is supported by the fact that it does not form an ethyl or methyl ether when it is crystallised from ethyl or methyl alcohol, neither does it form an acetone compound in the same way. However, should solasodine exist under certain conditions as a carbinolamine, the hydroxyl in this form must be tertiary as indicated and not secondary as in the two alternative positions, since solasodine and acetyl solasodine were recovered unchanged after attempted oxidation with potassium ferricyanide and chromic acid respectively.

The normal salts, with the exception of the nitrite, appear to be, not anhydro-salts, but derivatives of the carbinol-amine (cf. *ψ*-strychnine) and in some cases contain further water of crystallisation which is not lost on normal drying. This conclusion is based partly on analyses of salts of solasodine and those of solauricidine (see following paper). The results of catalytic hydrogenation with platinum oxide are also best explained on this basis. As mentioned previously, solasodine with this catalyst yields tetrahydrosolasodine (dihydro*chano*solasodanol), m. p. 286—288·5°, which still retains two oxygen atoms. If solasodine did not function as a carbinol-amine, reduction might be expected to give dihydrosolanidine, thus:

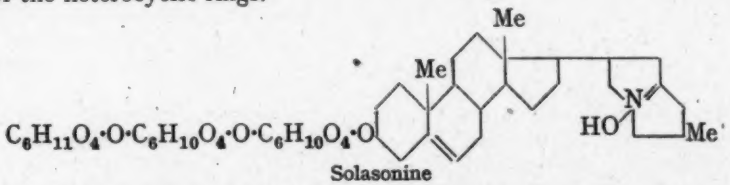


and it is therefore suggested that hydrogenation proceeds through the carbinol-amine by a type of Emde degradation as follows:



In dihydrosolasodine the ordinary carbon-to-carbon double bond has been saturated and the basic portion of the molecule still functions as a quaternary hydroxide, since the actions of hydrogen iodide and ethyl iodide both yield the same quaternary iodide, m. p. 284° (decomp.), which regenerates dihydrosolasodine on treatment with dilute aqueous ammonia.

Solasodiene on hydrogenation with a platinum oxide catalyst forms *hexahydrosolasodiene* (*dihydrochanosolasodan*), $C_{27}H_{47}ON$, m. p. 184—186°, which still retains one oxygen atom. It is suggested that here also hydrogenation proceeds through the carbinol-amine, saturation of the normal conjugated double bonds and fission of the heterocyclic rings.



As a basis for further degradative work we therefore propose the above quaternary hydroxide form for solasonine, and investigations on the heterocyclic portion of the molecule are in active progress.

There are marked differences in the chemical behaviour of the berberine type of alkaloids and ψ-strychnine and still further differences between ψ-strychnine and solasodine—differences which may possibly be due to the size of the rings concerned or more probably to the number of double bonds present.

Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329) has recorded a series of colour reactions of solasodine and solasodiene with reagents usually applied to sterols. As previously reported (*Nature*), it has now been found that the bases in this series give a series of beautiful colour reactions in acetic acid–sulphuric acid solution in the presence of substituted aromatic aldehydes, especially those substituted in the *p*-position. The addition of the aldehydes considerably modifies the colour reactions produced by acetic acid–sulphuric acid alone, which is a modified Liebermann reaction (*Ber.*, 1885, **18**, 1803).

An exceptionally fine play of colours is also given by solasodine in acetic acid–sulphuric acid solution in the presence of resorcinol; this serves as a very easy method of distinguishing solasodine from solanidine, which gives quite a different coloration.

An unsuccessful attempt has been made to evaluate these colour reactions by carrying out the reaction with sterol derivatives such as cholesterol and digitonin, with heterocyclic bases such as carbazole, pyrrole, and nicotine, and the alkaloid jacobine, which contains the pyrrolizidine nucleus similar to that now proposed for solasodine (cf. Henry "The Plant Alkaloids," 1939, pp. 636—642; Clemo and Metcalfe, J., 1936, 606; Prelog and Heinbach, *Ber.*, 1939, **72**, 1101). All these give characteristic intense colorations differing from those of solasodine or solanidine. We would suggest that other workers in a more fortunate position in regard to the variety of steroid compounds available might investigate these colour reactions further (cf. Woker and Antener, *Helv. Chim. Acta*, 1939, **22**, 1309; Scherrer, *ibid.*, p. 1329). The hydro-derivatives of solasodine give much less intense colorations, which are therefore connected with the unsaturated centre as well as the basic portion.

Tutin and Clewer (J., 1914, **105**, 565) isolated from *S. angustifolium* a glucosidic base, solangustine, which is hydrolysed by acid to glucose and solangustidine, $C_{27}H_{43}O_2N$. Since the latter is now isomeric with solasodine, the two aglycones are probably very closely related.

Experimental.

Extraction of Solasonine.—Besides the method described in Part I (preceding paper) for the isolation of solasonine the following wet process has been devised, obviating the use of alcohol. Green berries of *S. sodomæum* were minced and pressed, and the juice kept for 4—8 hours. The clear supernatant liquor was drawn off by suction and filtered in a gravity filter with frequent changes of the filter paper. The filtrate was boiled and similarly filtered while hot. The clear filtrate was boiled, and ammonia passed through it until it was alkaline; boiling was then continued for 5 minutes. After cooling, the granular precipitate was collected by suction, dissolved in 2% acetic acid, and reprecipitated with ammonia from the boiling solution. This treatment was continued until the material was pure; solasodine was then obtained as described in Part I. Crystallisation from aqueous alcohol or dioxan effects little change in the m. p. of the crude hydrolysis product, which contains solasodiene, but after crystallisation from methyl alcohol the m. p. rises sharply and has now been raised to 200·5—202·5°.

In addition to the analyses for solasonine and solasodine recorded in Part I analyses already recorded (Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404, 2467) have been recalculated on a C_{27} basis for solasodine.

Solasonine (*ex S. aviculare*) (Found: C, 60·2; H, 8·4; N, 1·5. Calc. for $C_{45}H_{73}O_{16}N,\frac{1}{2}H_2O$: C, 60·5; H, 8·3; N, 1·6%).

A sample of solasonine kindly presented by Professor Oddo was submitted for analysis without preliminary drying (Found: C, 56·1, 56·0; H, 8·6, 8·7; N, 1·8, 1·7. Calc. for $C_{45}H_{73}O_{16}N,4\frac{1}{2}H_2O$: C, 56·0; H, 8·5; N, 1·45%).

Solasodine (*ex S. aviculare*) (Found: C, 78·3; H, 10·4; N, 3·3. Calc. for $C_{27}H_{43}O_2N$: C, 78·54; H, 10·5; N, 3·4%).

A sample of solasodine from Professor Oddo was analysed without preliminary drying (Found: C, 75·2, 75·1; H, 10·5, 10·6; N, 3·3, 3·4. Calc. for $C_{27}H_{43}O_2N,H_2O$: C, 75·2; H, 10·4; N, 3·2%).

M (micro-Rast), 388, 375. Calc. for $C_{27}H_{43}O_2N$: *M*, 413.

In a determination of active hydrogen (Zerewitinoff method) in anisole solution, 66·89 mg. of solasodine, previously dried for several hours in a high vacuum at 100° over phosphoric oxide, evolved 7·30 c.c. of methane at 25°/750 mm., corresponding to 1·91 atoms of active hydrogen per mole. By working up the reaction mixture in the usual way, pure solasodine was recovered.

Determinations of the CMe value (Kuhn–Roth method) for solasodine gave 2·39 and 2·12 groups per mole. In *M*/5000-alcoholic solution solasodine gives general absorption only and therefore does not contain a centre capable of producing a selective effect.

Acetylsolasodine.—A mixture of solasodine (500 mg.), dry pyridine (5 c.c.), and acetic anhydride (1 c.c.) was refluxed for 2 hours. After cooling, the mixture was poured into water and made alkaline with ammonia. The precipitated acetyl derivative (520 mg.), after successive crystallisation from dioxan–water, ethyl acetate,

and ethyl acetate–alcohol, formed narrow plates, m. p. 195° (Found: C, 76·6; H, 10·4; N, 3·4. Calc. for $C_{39}H_{45}O_3N$: C, 76·5; H, 9·9; N, 3·1%). Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329) records m. p. 193—194°. The acetyl derivative was immediately soluble in dilute acetic acid and did not give an immediate precipitate with digitonin.

3 : 5-*Dinitrobenzoylsolasodine.*—Solasodine (100 mg.), dissolved in dry pyridine (1 c.c.), was refluxed for ½ hour with a solution of 3 : 5-dinitrobenzoyl chloride (200 mg.) in dry pyridine (3 c.c.). The precipitate which formed was collected after dilution with water, treated with dilute aqueous ammonia, and crystallised from alcohol, forming yellowish needles, m. p. 191·5—193°.

Phenyl *iso*thiocyanate failed to form a derivative with solasodine, and α-naphthyl *iso*cyanate brought about dehydration, yielding *s*-dinaphthylurea and a basic product, m. p. 165°, undepressed on admixture with solasodiene.

Action of Methyl Iodide and Ethyl Iodide on Solasodine.—When solasodine (200 mg.) and methyl iodide (1 c.c.) in dry xylene (2 c.c.) were heated to boiling, a colourless precipitate formed within a few minutes (yield, 250 mg. after 2 hours). The product crystallised from methyl alcohol–ether in colourless prisms, m. p. 285—286° (decomp.), undepressed by solasodine hydriodide, m. p. 291° (decomp.) (Found: C, 59·2; H, 8·1; I, 23·4. Calc. for $C_{27}H_{43}O_2N,HI$: C, 59·9; H, 8·1; I, 23·5%).

The action of ethyl iodide on solasodine (previously dried for several hours over phosphoric oxide at 110°) under similar conditions also gave the hydriodide, m. p. 284° (decomp.), undepressed by the authentic hydriodide (Found: C, 60·6; H, 8·2; N, 2·7; I, 24·5, 22·1. Calc. for $C_{27}H_{43}O_2N,HI$: C, 59·9; H, 8·1; N, 2·6; I, 23·5%). The iodine values recorded here represent ionic iodine obtained by direct titration according to Leipert's method (Pregl Festschrift, 1929, p. 266).

In both cases, treatment with hot dilute aqueous ammonia, followed by crystallisation from methyl alcohol, regenerated pure solasodine, m. p. 198—200°, undepressed by an authentic specimen.

Action of Nitrous Acid on Solasodine.—Sodium nitrite (170 mg.), dissolved in the least amount of water, was added dropwise to a solution of solasodine (500 mg.) in cold alcohol (5 c.c.) and glacial acetic acid (0·25 c.c.). The gelatinous precipitate formed was collected and crystallised repeatedly from 80% alcohol and finally from alcohol to yield the quaternary *nitrite*, m. p. 260·5—262·5° (decomp.) (Found: C, 73·2; H, 9·6; N, 6·2. $C_{27}H_{42}O_3N_2$ requires C, 73·3; H, 9·6; N, 6·3%). Oddo and Caronna (*loc. cit.*) record m. p. 260° (decomp.) for this product, referred to as "azosolasodine." Treatment with hot dilute aqueous ammonia regenerated solasodine.

Action of Thionyl Chloride on Solasodine.—Dry solasodine (1·16 g.), dissolved in dry pyridine (43 c.c.), was cooled in ice, and redistilled thionyl chloride (1 g.) added slowly; a precipitate formed immediately. After standing at 0° for 17 hours, the product was poured into water (200 c.c.). The product so formed was crystallised repeatedly from 80% alcohol to give solasodine hydrochloride in needles, m. p. 307—308° (decomp.) (Found: C, 70·5, 70·4; H, 9·9, 9·9; Cl, 7·5, 7·5. Calc. for $C_{27}H_{43}O_2N,HCl,\frac{1}{2}H_2O$: C, 70·6; H, 9·9; Cl, 7·7%). The product gave the test for ionic halogen with silver nitrate and after treatment with hot dilute aqueous ammonia regenerated solasodine, which crystallised from 80% alcohol in hexagonal plates, m. p. 199—200°, undepressed by an authentic specimen.

Hydrogenation of Solasodine.—(a) *With a palladium–norite catalyst.* Solasodine (500 mg.), dissolved in alcohol, was subjected to hydrogenation at the ordinary temperature and pressure with a palladium–norite catalyst freshly prepared from palladium chloride (50 mg.) and ignited norite (500 mg.). Hardly any absorption occurred in 5 hours. To test the activity of the catalyst, cinnamic acid (250 mg.) in alcoholic solution was added. Absorption was then extremely rapid, the theoretical amount of hydrogen required for the cinnamic acid being absorbed within 5 minutes; absorption then proceeded more slowly for some hours. The catalyst was removed, the filtrate concentrated somewhat, and the hot solution made alkaline with ammonia. *Dihydrosolasodine* crystallised in needles; after recrystallisation from 75% alcohol and dioxan–water it formed hexagonal plates, m. p. 208·5—210·5° (Found: C, 78·3; H, 10·9. $C_{27}H_{45}O_2N$ requires C, 78·0; H, 10·9%). $[\alpha]_D^{25°}$ − 63·5° (l = 0·5 dcm., c = 8·824 in chloroform). Dihydrosolasodine was also obtained more conveniently in glacial acetic acid solution at 45 lb. pressure. In this case, the acetic acid solution was concentrated by distillation in a vacuum before treatment with ammonia. Dihydrosolasodine did not give the test with Denigès's reagent for tertiary alcohols.

The hydriodide, precipitated in colourless prisms on addition of a concentrated solution of potassium iodide to dihydrosolasodine dissolved in alcohol–acetic acid, had m. p. 284° (decomp.) after recrystallisation from alcohol.

(b) *With a platinum oxide catalyst.* Solasodine could not be hydrogenated in alcoholic solution at atmospheric pressure with Adams's platinum oxide catalyst, acid conditions again being necessary.

Solasodine (400 mg.), dissolved in a mixture of alcohol (5 c.c.) and glacial acetic acid (1 c.c.), was hydrogenated at 46 lb. pressure for several hours in the presence of Adams's catalyst (200 mg.). The solution was then decanted from the catalyst, concentrated somewhat, and made alkaline with ammonia. The product could be separated by repeated crystallisation into possibly dimorphic forms, (i) thick plates, m. p. 292·5—296·5°, from alcohol–water, and (ii) octahedral crystals from dioxan–water, m. p. 285—291°, not depressed on admixture with (i). Rochelmeyer records m. p. 285·5—288° for this tetrahydro-derivative (Found: C, 77·8,

77·9; H, 11·2, 11·3. Calc. for $C_{27}H_{47}O_2N$: C, 77·6; H, 11·35%). Hydrogenation could also be effected in glacial acetic acid solution. Tetrahydrosolasodine (dihydrosolasodanol) does not react with tetranitromethane or with antimony trichloride.

Action of Ethyl Iodide on Dihydrosolasodine.—Dihydrosolasodine (100 mg.), dissolved in dry benzene or xylene (2 c.c.), was refluxed for 15 hours with ethyl iodide (1 c.c.). The colourless precipitate which formed crystallised from 50% alcohol in needles, m. p. 281° (decomp.), raised to 283° on admixture with the hydriodide. Treatment of a suspension of the product (80 mg.) in water (6 c.c.) with amomnia at 100° for 2 hours regenerated dihydrosolasodine, which crystallised from alcohol in plates, m. p. 209·5—211·5°, undepressed by an authentic specimen.

Bromination of Solasodine.—(a) *In chloroform.* When bromine in chloroform solution was added dropwise to a cooled solution of solasodine (400 mg.) in the same solvent, decoloration ceased only when three atoms of bromine had been added. The chloroform was distilled off in a vacuum; the residue crystallised on trituration with alcohol. When recrystallised from a mixture of water, alcohol and acetone containing a little hydrobromic acid, it formed colourless needles, m. p. 303° (decomp.).

(b) *In glacial acetic acid.* 8·5 C.c. of a solution of bromine in glacial acetic acid (containing 160 mg., 1 mol.) were added dropwise to a cooled solution of solasodine (431 mg., 1 mol.) in the same solvent (4 c.c.). Decoloration occurred almost immediately and addition of a further 0·5 c.c. of the bromine solution gave a permanent coloration. Sodium bromide (515 mg., 5 mols.) was then added, followed by water until precipitation of the *hydrobromide* was complete. The product (450 mg.), on crystallisation from a mixture of water, alcohol, and acetone containing a little hydrobromic acid, formed colourless needles, m. p. 302° (decomp.), undepressed by the bromination product obtained in (a). The product gave an immediate test for ionic bromine with silver nitrate solution (Found: Br, 24·5. $C_{27}H_{43}O_2NBr,HBr$ requires Br, 27·9%).

Dehydration of Solasodine.—Solasodine could not be dehydrated satisfactorily by heating with anhydrous formic acid or with potassium hydrogen sulphate, but was smoothly dehydrated with methyl- or ethyl-alcoholic hydrogen chloride. Solasodine (200 mg.) was dissolved in cold methyl alcohol (20 c.c.), and dry hydrogen chloride passed in until the mixture had increased in weight by 20%. When heated to 100°, the solution cleared and later needles of solasodiene hydrochloride separated, m. p. 318° (decomp.) after washing with ether. When a suspension of the hydrochloride was treated with hot dilute aqueous ammonia and cooled, solasodiene was obtained, which after repeated crystallisation from aqueous dioxan, methyl alcohol and ethyl alcohol of various concentrations formed plates of constant m. p. 169·5—170·5° (Found: C, 82·0; H, 10·5; N, 3·6. Calc. for $C_{27}H_{41}ON$: C, 82·0; H, 10·5; N, 3·5%). $[\alpha]_D^{25°}$ − 86·9°(l = 0·5 dcm., c = 2·6016 in chloroform). In determinations of active hydrogen (Zerewitinoff method) in anisole solution, 49·43 mg. and 41·78 mg. of solasodiene evolved 2·96 c.c. and 2·55 c.c. of methane at N.T.P. respectively, corresponding to 1·04 and 1·08 atoms of active hydrogens per mole. Solasodiene gave a yellow coloration with tetranitromethane, an immediate intense red coloration with antimony trichloride in chloroform solution, and a positive Rosenheim reaction for conjugated double bonds.

Solasodiene (7·1 mg.) in alcohol (4·5 c.c.) was added to digitonin (31·4 mg.) in warm water (1·5 c.c.); a precipitate did not form in 48 hours.

A mixture of solasodiene (100 mg.) in benzene (2·5 c.c.) and thrice sublimed maleic anhydride (1 g.), heated for 24 hours at 100° with exclusion of moisture, became deep red. A crystalline adduct could not be obtained (cf. Rochelmeyer, *Arch. Pharm.*, 1937, **275**, 336).

In alcoholic solution (M/5000) solasodiene exhibited a marked band at λ 2345 A., log ε 4·44, together with an inflexion at *ca.* λ 2400 A., log ε *ca.* 4·17, consistent with the presence of two conjugated double bonds distributed over two rings (cf. Rochelmeyer, *Arch. Pharm.*, 1939, **277**, 329; *Ber.*, 1938, **71**, 226).

Hydrogenation of Solasodiene.—Solasodiene (1 g.) in glacial acetic acid (40 c.c.) was hydrogenated at 48 lb. pressure in the presence of platinum oxide (0·2 g.) for 5 hours. The catalyst was then filtered off, most of the solvent removed by vacuum distillation, and the residue made alkaline with ammonia and heated for 3 hours at 100°. After crystallisation from dioxan–water and aqueous alcohol the product formed flat needles, m. p. 184—186° (Found: C, 80·8, 80·85; H, 11·85, 11·9. $C_{27}H_{47}ON$ requires C, 80·7; H, 11·8%). $[\alpha]_D^{25°}$ − 18° (l = 0·5 dcm., c = 6·424 in chloroform).

Hexahydrosolasodiene (*dihydro*chano*solasodan*) did not react with tetranitromethane, antimony trichloride or Denigès's reagent.

Bromination of Solasodiene.—A solution of bromine in chloroform was gradually added to a solution of solasodiene (100 mg.) in the same solvent (2 c.c.) at 0°. Decoloration ceased after the addition of 3 atoms of bromine; the solvent was then evaporated, yielding a brown product which quickly darkened in air. One drop of concentrated hydrobromic acid was added to a solution of the product in alcohol, followed by addition of water until precipitation occurred. The mixture cleared on warming and, on cooling, colourless crystals formed which after recrystallisation from 50% alcohol formed flat needles, m. p. 205—209°. The compound rapidly darkened in air and was not analysed.

When bromine in acetic acid solution was added dropwise to a cooled solution of solasodiene (200 mg.) in the same solvent, decoloration occurred almost instantly until two atoms of bromine had been added, absorption then taking place very slowly. A small amount of precipitate formed, which was not increased by addition

of water, and addition of sodium bromide solution failed to precipitate an insoluble hydrobromide as in the case of the bromination of solasodine.

Oxidation of Solasodine with Copper Powder.—A mixture of solasodine (200 mg.) and copper powder (300 mg.) was heated in a metal bath at 10 mm. pressure, a water-cooled finger condenser being placed about 1 cm. above the mixture. Above its m. p. the solasodine partly sublimed, but above 250—285° evolution of gas occurred. The sublimate was mixed with the residual copper, and the process repeated at 250—255°/0·01—0·02 mm. The brown glassy sublimate (180 mg.), when added to a 1% solution of *m*-dinitrobenzene and made alkaline with sodium hydroxide solution, gave a violet coloration. The product became crystalline on trituration with acetone, and on recrystallisation from the same solvent a small amount of unchanged solasodine was obtained and another product, m. p. 186°, corresponding to that of solasodenone obtained by Rochelmeyer (*loc. cit.*) by the oxidation of solasodine with Oppenauer's reagent.

Attempted Oxidation of Acetylsolasodine (With J. J. CARROLL).—Acetylsolasodine (1·47 g.) was dissolved in glacial acetic acid (30 c.c.) added dropwise; after 4 days the colour had changed from golden-yellow to dark green. Ammonia was added to the solution after dilution with water (120 c.c.) and the product was converted in alcoholic solution into the hydrochloride, which, on cooling, formed colourless crystals, m. p. 314°, of acetylsolasodine hydrochloride. The free base, obtained in the usual way by treatment with ammonia, had m. p. 193—195°, undepressed by admixture with the starting material.

Colour Reactions of Solasodine and Related Compounds.—When concentrated sulphuric acid (1 c.c.) is carefully added to a solution of solasonine or solasodine in hot alcohol (1 c.c.), a characteristic, intense greenish-yellow fluorescence is produced similar to that of heavy lubricating oil. This coloration is not given by solanine or solanidine.

A few mg. each of solasodine and the following aromatic aldehydes were mixed with concentrated hydrochloric acid and boiled. The colours produced were as follows: *p*-dimethylaminobenzaldehyde, pink (stable); vanillin, green—colourless—pink-bluish pink; piperonal, green—fades—bluish-pink on standing; *p*-nitrobenzaldehyde, faint pink, quickly fading; anisaldehyde, greenish-blue; *p*-hydroxybenzaldehyde, greenish-blue.

Benzaldehyde, salicylaldehyde, *o*-nitrobenzaldehyde and glucose were without action. Blank tests without the alkaloid were negative, and carbazole, indole, and nicotine with the same reagents gave as a rule magenta, scarlet and crimson colorations respectively.

Much more intense and more stable colorations were given when a few mg. of solasodine or a related compound and the following aldehydes were dissolved in acetic acid (1—2 c.c.), to which sulphuric acid (1—2 c.c.) was then carefully added. Characteristic colours developed at the interface, which changed on mixing, but the full variety of colour changes did not develop until the mixture was heated; many of them disappeared on dilution. The most intense and characteristic colour reaction of solasodine itself is given with resorcinol in the same acid solvent.

	Solasodine.	Solanidine.
p-Hydroxybenzaldehyde	Red/violet dichroic-purple-blue-pale violet/chocolate dichroic	Red-red/slight violet dichroic
Anisaldehyde	Red/green dichroic-violet/green dichroic-blue-purple	Red/greenish dichroic-crimson/slight blue dichroic
Vanillin	Red-violet-sepia (or depending on conditions of heating, green-blue-violet)	Dark brown-red-wine/slight dichroism of different shade
Resorcinol	Brown-brownish green-blue-purple-purple/violet dichroic-magenta-red/violet dichroic with chocolate fluorescence-cerise/brown fluorescence	Brown/green fluorescence

	Dihydrosolasodine.	Solasodiene.	Dihydro*chano*solasodan.
p-Hydroxybenzaldehyde	Brown-green-bluish green-blue-fades	Purple-violet-blue fades to colourless/light brown dichroic-brownish red	Red-deep red-brown
Anisaldehyde	Greenish brown-green fades to a dirty brown/colourless dichroic-red dichroic-intense crimson	Violet-purple-blue-bluish green-green-purple.	Green/brown dichroic-red/green dichroic-crimson-crimson purple
Vanillin	Yellowish green-green-dirty brown-brownish green-brown	Dirty brown-green-blue (fades)-light purple-dirty brown	Brown-dark brown
Resorcinol	Brown/green fluorescence-pinkish red/green fluorescence-light brown/slight green fluorescence	Green-blue-purple/brown fluorescence-red/brown fluorescence-red	Darkens with a green fluorescence

Piperonal, *p*-dimethylaminobenzaldehyde, *p*-methoxybenzaldehyde and *p*-nitrobenzaldehyde also give a similar series of colour reactions different in each case. Solasodine alone with the acetic acid–sulphuric acid reagent gives a brown/violet dichroic-violet-wine-brown coloration, and the aldehydes themselves either do not give a coloration or only brown to red colorations with the exception of anisaldehyde, which gives the following series of colours, brownish green-brown-red/green dichroic-crimson-crimson/slight purple dichroic.

For comparison the same colour reactions were carried out with cholesterol, digitonin, jacobine, carbazole, pyrrole and nicotine. In each case different colorations were produced, but the most intense colorations

were brought about with *p*-hydroxybenzaldehyde and anisaldehyde and only these and those with resorcinol are recorded.

	Cholesterol.	Digitonin.	Jacobine.
p-Hydroxybenzaldehyde	Crimson-violet-purple	Brown-red-brown	Yellow-brown-red-dark brown
Anisaldehyde	Purple	Brown-red-brown	Brown/green dichroic-brown-red-dark brown-intense purplish red
Resorcinol	Brown-red-brown	Red/brown dichroic-red brown	Brown-red-red/green fluorescence
	Carbazole.	Pyrrole.	Nicotine.
p-Hydroxybenzaldehyde	Crimson	Very intense reddish brown	Red
Anisaldehyde	Crimson-violet	Very intense reddish brown	Red
Resorcinol	Light brown	Light brown	Light brown

Piperidine with the same reagents gives no coloration or only a light brown coloration.
The carbon, hydrogen and nitrogen analyses are by Dr.-Ing. A. Schoeller and Dr. Burger.

Grateful thanks are due to Mr. R. G. Cooke through the courtesy of Professor A. K. Macbeth for the measurement of the absorption spectra, to Mr. C. W. Brandt, M.Sc., for a sample of jacobine, and to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for grants.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, January 30th*, 1941.]

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3. Solanum *Alkaloids. Part III. The Alkaloids from* Solanum auriculatum.

By R. CULFORD BELL, LINDSAY H. BRIGGS, and JOHN J. CARROLL.

Alcoholic extraction of the dried berries of *S. auriculatum* leads to the isolation of a glycoalkaloid, m. p. 270° (decomp.), which on hydrolysis yields a mixture of sugars (see following paper) and an aglycone, m. p. 222—223°. The names *solauricine* and *solauricidine* are suggested for these respective compounds and evidence is adduced that solauricidine is neither identical with nor a dimorphic form of solasodine but is extremely closely related to it in both physical and chemical properties. No structural differences between solauricidine and solasodine have yet been found. The separation of alkaloid material from the juice of the green berries affords a product, m. p. 269—270° (decomp.), which on hydrolysis gives a mixture of bases consisting mainly of solasodine with a smaller amount of solauricidine. Both the latter bases occur in dimorphic forms, the respective pairs being indistinguishable.

THE green berries of *Solanum auriculatum* were first investigated by Greshoff (*Ber.*, 1890, **23**, 3541; *Ber. deut. pharm. Ges.*, 1899, **9**, 214), who reported that they were rich in "solanine." More recently, Anderson and Briggs (J., 1937, 1036) isolated a colourless, crystalline glycoalkaloid, m. p. 272°, with colour reactions similar to those of solasonine. On hydrolysis with alcoholic hydrogen chloride, an aglycone was obtained, m. p. 216—219°, which raised the melting point of solasodine but depressed that of solanidine. Since it gave the same colour reactions as solasodine and afforded derivatives with the same melting point as those prepared from solasodine and admixture of respective pairs gave no depression, it was concluded that the aglycone was an isomorphic (more correctly dimorphic) form of solasodine.

This investigation has been continued and further evidence now indicates that the aglycones from *S. auriculatum* and solasodine are neither identical nor dimorphic forms, but are isomeric and extremely closely related in both physical and chemical properties, the only major difference so far observed being in their melting points. We suggest the names *solauricine* and *solauricidine* for the glucoside and aglycone respectively.

Analyses of solauricine and solauricidine as well as derivatives of the latter support formulæ $C_{45}H_{73}O_{16}N$ and $C_{27}H_{43}O_2N$ for these respective bases, which are the same as those suggested for solasonine and solasodine respectively (preceding paper). The melting point of the aglycone has been raised to 220—223°, which is considerably higher than that of the purest specimen of solasodine yet obtained, m. p. 200·5—202·5° (Part II). There is no doubt in our minds as to the purity of these specimens, whose homogeneity is also indicated by the crystallographic data (pp. 14, 15). From solasodine and solauricidine as well as the corresponding glycoalkaloids a number of derivatives have been prepared for comparison and the respective pairs almost without exception have melting points within a few degrees and give no depression on admixture. To avoid differences in melting point due to the rate of heating (cf. Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404), in most cases both the melting points of the respective pairs and the mixture have been determined at the same time in Mason's melting

point apparatus (electrically heated copper block). Where a figure is not given in the following table, it indicates that the mixed melting point was taken separately, but in each case no depression was observed.

Derivative.	Solasonine, m. p.	Solauricine, m. p.	Mixed m. p.
Glycoalkaloid	276°	270°	272°
Picrate	197	185	184
Picrolonate	231	232	—
Aglycone	198	219	208—211
Hydrochloride	314·5—315	313—313·5	313·5—314
Hydrobromide	299	309	—
Hydriodide	288	285	286
Sulphate	293	?	—
Nitrate	269	266—267°	—

Derivative.	Solasonine, m. p.	Solauricine, m. p.	Mixed m. p.
Aglycone			
Nitrite	260·5—262·5°	260—264°	—
Picrate	144	141	142°
Picrolonate	232	234	232
Tartrate	220	222	221
Oxalate	245—246	238	239
o-Nitrobenzoate	222	220	—
Acetyl derivative	195	197—203	—

(All the above compounds with the exception of the aglycones and their acetyl derivatives melt with decomposition.)

Whether the respective aglycones are dimorphic forms and the salts identical as the results in the above table would indicate has been tested experimentally in various ways.

Measurements of the optic axial angles of the crystals of the aglycones showed appreciable differences (solasodine, $2V = 74° \pm 2°$, the optic sign is positive in all cases discussed in this paper; solauricidine, $2V = 56° \pm 2°$; see later, however), and the optic axial angles of the corresponding hydrochlorides are indistinguishable, $2V = 85° \pm 5°$.

Dimorphism should disappear both in solution and in the vapour state. In solution, the specific rotations of the aglycones differ somewhat, solasodine — 80·4°, solauricidine — 89·9°, but those of the hydrochlorides are almost the same within experimental error (— 70·5° and — 68·2° respectively). When Halford's procedure (*J. Amer. Chem. Soc.*, 1931, **53**, 2640) for the identification of closely related compounds was applied to solasodine and solauricidine in boiling acetone solution, in only one out of five experiments was a rise of boiling point observed, and the hydrochlorides showed no effect on each other in boiling ethyl-alcoholic solution. In this case, owing to the high molecular weights of the substances involved and the lack of high solubility in the solvents concerned, any elevation of boiling point to be expected in the case of non-identical compounds would be small and possibly within the experimental error.

In the vapour state the evidence against dimorphism is conclusive. When solasodine and solauricidine are sublimed at low pressures, the melting points of the sublimed crystals are unaltered.

Should the aglycones be dimorphic, one form should be more stable than the other and the two interconvertible under appropriate conditions. In all our experiments, extending over some years and in which five independent workers have been involved, we have always obtained solauricidine, m. p. *ca.* 220°, on hydrolysis of the glycoalkaloid obtained by alcoholic extraction of the dried berries of *S. auriculatum* and during a similar period, often in the same room and using identical methods and solvents, we have always obtained solasodine, m. p. 198—200°, from *S. sodomæum* or *S. aviculare* (cf. Part I, this vol., p. 1) without any case of interconversion. Attempts to convert one form into the other by seeding during crystallisation have been unsuccessful, the product having an intermediate melting point depending on the amount of seeding crystals used. A similar result is obtained when the respective bases are kept above their melting points for some time and the melting points of the cooled solids redetermined, no appreciable change from the original melting points being observed.

Should the salts of the bases be identical, as some of the above evidence would indicate, then one and the same base should be obtained by the action of ammonia. When this has been done in ordinary preparative work and in experiments carried out under exactly similar conditions, the corresponding aglycones of different melting points have invariably been obtained.

Despite some evidence to the contrary the main weight of evidence definitely points to the conclusion that solauricidine is neither identical with nor a dimorphic form of solasodine. With this view, further experiments were undertaken in order to find the seat of such differences, but so far no structural differences have been discerned. The aglycone gives the analytical figures required for $C_{27}H_{45}O_3N$ when dried in the usual way and for $C_{27}H_{43}O_2N$ only after vigorous drying. Solauricidine contains one hydroxyl group on the C_3 atom in the *cis*-position to the angular methyl group on C_{10}, since it gives a precipitate with digitonin and forms an acetyl derivative, m. p. 197—203°, soluble in dilute acids, which no longer gives a precipitate with digitonin. The remaining oxygen is present attached to the nitrogen as a quaternary hydroxide or as the related carbinolamine, since the actions of methyl iodide and ethyl iodide both give the hydriodide, from which the aglycone is regenerated on treatment with dilute aqueous ammonia (see also Part II). Since the aglycone is a quaternary hydroxide, the salts would be expected to occur as anhydro-salts (cf. berberine and related alkaloids).

Analyses of the salts indicate, however, that (with the exception of the nitrite) actually in some cases further firmly bound water of crystallisation not removed on drying is present which masks any anhydrosalt formation (cf. ψ-strychnine). The action of nitrous acid yields a compound, $C_{27}H_{42}O_3N_2$, m. p. 260—264°, which, as in the case of solasodine, we regard as a quaternary nitrite, the only true anhydrosalt yet obtained in this series, since it regenerates solauricidine on treatment with dilute aqueous ammonia. Solauricidine is unsaturated, giving the usual tests for unsaturation, and catalytic hydrogenation with palladium–charcoal catalyst yields a hydro-derivative, m. p. 221·5—227·5°, which differs from dihydrosolasodine, m. p. 208·5—210·5°. The investigation of solauricidine is being continued.

Isolation of the alkaloid from the undried fruit of *S. auriculatum* by the more convenient and cheaper process described in Part II has given different results from those obtained by alcoholic extraction methods. The glycoalkaloid isolated by this process had m. p. 269—270° (decomp.), but was not rigidly purified. Hydrolysis with either 2% hydrochloric or sulphuric acid gave a crude amorphous material, m. p. 219°, but when crystallised from 80% alcohol, however, the substance melted at 184—186°. Only after a very lengthy series of crystallisations from different solvents, have two products been obtained, one, m. p. 198—200°, and the other (very small amount), m. p. 213—217°. These products are almost undoubtedly solasodine and solauricidine. When the hydrochloride obtained in the hydrolysis of the glycoalkaloid isolated above is rigidly purified and then converted into the free base, pure solasodine, m. p. 198—200°, is obtained after a single crystallisation. The hydrochloride, sulphate, nitrite and acetyl derivative of the material, m. p. 198—200°, all agree in melting point with the respective compounds of solasodine and give no depression on admixture with authentic specimens. Since, however, mixed melting points do not seem to be valid criteria of identification in this series, the free bases were submitted for measurement of their optic axial angles, with unexpected results. The purest specimens of solasodine, solauricidine (obtained by the alcoholic extraction method), and the product, m. p. 198—200°, isolated in the last instance, were all recrystallised from the same sample of methyl alcohol and then had m. p. 199—202°, 200—223°, and 199·5—202° respectively. The optic axial angles of the first two compounds, which had previously given values $2V = 74° \pm 2°$ and $55° \pm 2°$ respectively, as well as of the last material, now all had the same value within experimental error, $2V = 73°$, 73·5° and 73·5° respectively, *i.e.*, the value previously obtained only for solasodine. These and the earlier measurements were taken by Dr. F. J. Turner, Otago University, to whom we are greatly indebted. All three compounds were now recrystallised by Mr. N. E. Stace, M.Sc., a co-worker in Part II of this series, at Otago University again from methyl alcohol; the melting points then remained practically unchanged. However, the optic axial angles were again all the same but with a different value, $2V = 54°$, 58°, and 54° respectively, *i.e.*, the value previously obtained only for solauricidine. It is apparent, therefore, that both solasodine and solauricidine occur in dimorphic forms, the optical axial angles of each respective dimorphic form obtained from solasodine or solauricidine being indistinguishable. The only explanation which can be given for the conversion of one crystalline form into the other when crystallised from the same solvent is the presence of different nuclei in the atmosphere, an explanation which has been offered by Dewar, Morrison, and Read for a similar phenomenon with benzylidene-*dl*-piperitone (J., 1936, 1598).

Experimental.

Extraction of the Alkaloid with Alcohol.—The minced and dried green berries of *S. auriculatum* were continuously extracted with alcohol containing 1% of acetic acid in an all-metal extractor of the Soxhlet principle capable of treating 56 lb. of material, and the extract worked up as described in Part I. *Solauricine* was thus obtained in colourless plates, m. p. 269·5—270° (decomp.) after fifteen successive crystallisations from 75% ethyl alcohol or 80% dioxan–water (Found in dried material: C, 58·4; H, 8·2; N, 2·2, 2·2. $C_{45}H_{73}O_{16}N,2H_2O$ requires C, 58·8; H, 8·4; N, 1·5%).

The colour reactions of solauricine are the same as those of solasonine (Part II). The picrate and the picrolonate were prepared by heating the components in alcoholic solution and recrystallised from 80% alcohol.

The pure solauricine was then hydrolysed by heating with 2% hydrochloric or sulphuric acid in the water-bath for 3 hours, the hydrochloride or sulphate of solauricidine separating from the hot solution in a crystalline condition. In some cases the salts were further purified by several recrystallisations from 80% alcohol, but in most cases the crude salts were converted into the free *base* by treatment in aqueous suspension with excess of ammonia at 100° for some hours, with substantially the same results. The material thus formed had m. p. 218—220° and after repeated crystallisation from 80% alcohol and methyl alcohol it formed colourless hexagonal plates, m. p. 220—223° (Found in dried material: C, 74·6, 74·9; H, 10·4, 10·3; N, 3·3. $C_{27}H_{43}O_2N,H_2O$ requires C, 75·1; H, 10·5; N, 3·2%. Found for a different sample more vigorously dried: C, 77·7; H, 10·3. $C_{27}H_{43}O_2N$ requires C, 78·45; H, 10·4%). $[\alpha]_D^{250°} - 89·8°$ ($l = 1$ dcm., $c = 0·2560$ in methyl alcohol). The colour reactions are the same as those recorded for solasodine (Part II).

The salts were all formed by addition of the components in alcoholic solution; they were recrystallised from 80% alcohol and dried for analysis. The melting points are recorded on p. 13.

Solauricidine hydrochloride (Found: C, 66·9; H, 10·0; N, 3·95. $C_{27}H_{43}O_2N,HCl,2H_2O$ requires C, 66·8; H, 9·9; N, 2·9%). $[\alpha]_D^{250°}$ − 68·2° (l = 2 dcm., c = 0·4248 in methyl alcohol).

Solauricidine sulphate (Found: C, 61·95; H, 9·5; N, 2·8. $C_{27}H_{43}O_2N,H_2SO_4,\frac{1}{2}H_2O$ requires C, 62·3; H, 8·8; N, 2·7%).

Solauricidine hydriodide (Found: C, 60·0; H, 8·2; N, 2·5. $C_{27}H_{43}O_2N,HI$ requires C, 59·9; H, 8·1; N, 2·6%).

Solauricidine picrate (Found: C, 60·2; H, 7·1; N, 8·8. $C_{27}H_{43}O_2N,C_6H_3O_7N_3,H_2O$ requires C, 59·9; H, 7·4; N, 8·5%).

Solauricidine nitrite (Found: C, 72·8; H, 9·5. $C_{27}H_{42}O_3N_2$ requires C, 73·3; H, 9·5%). On treatment in aqueous suspension with ammonia, the nitrite (prepared as described in Part II) regenerated solauricidine, m. p. 218—221·5°.

Digitonin (13·5 mg.), dissolved in warm water (2 c.c.), was added to a solution of solauricidine (4·5 mg.) in warm alcohol (2 c.c.); an insoluble digitonide (15·5 mg.) separated on standing.

The acetyl derivative, obtained quantitatively as described in Part II for solasodine, after repeated crystallisation from ethyl acetate and ethyl acetate–alcohol formed needles, m. p. 197—203°. It dissolved immediately in dilute acetic acid and did not give a precipitate with digitonin.

The action of methyl or ethyl iodide on solauricidine in xylene solution afforded in both cases solauricidine hydriodide, m. p. 285° (decomp.) (cf. Part II), undepressed by an authentic specimen. It regenerated solauricidine on treatment with dilute aqueous ammonia.

Hydrogenation of Solauricidine.—A solution of solauricidine (300 mg.) in glacial acetic acid (6 c.c.) was hydrogenated at 45 lb. pressure in the presence of a palladium–charcoal catalyst (300 mg.) for 24 hours. The catalyst was removed, and the filtrate diluted with an equal volume of water and treated with excess of ammonia at 100° for 6 hours. The colourless product (265 mg.), after two recrystallisations from alcohol containing a drop of concentrated aqueous ammonia, formed thin plates, m. p. 221·5—227·5°, giving a negative test with antimony trichloride in chloroform solution. This material was unfortunately lost during a subsequent recrystallisation—the experiment has not yet been repeated, as the hydrogenation was carried out on the last quantity of solauricidine at our disposal.

Application of Halford's Procedure for the Identification of Solauricidine.—The b. p. of acetone was determined in the usual apparatus and again after the addition of excess of solasodine to form a saturated solution. Solauricidine was then added, and the boiling point redetermined, 10—15 minutes usually being allowed for the attainment of equilibrium. The experiment was then repeated in the reverse order of addition. In four out of five separate experiments the b. p. did not vary by 0·01°, but in one case a rise of 0·08° was observed. When the procedure was applied to the hydrochlorides in boiling ethyl alcohol, in two experiments where the additions were reversed the b. p. did not alter by 0·001°.

Extraction of the Alkaloid by Dilute Acetic Acid.—The improved process for the isolation of the alkaloid from the juice of the green berries as described in Part II yielded in this case a crystalline glycoalkaloid, m. p. 269—270° (decomp.). This was assumed to be solauricine and was hydrolysed directly with either 2% hydrochloric or sulphuric acid, yielding the insoluble hydrochloride or sulphate respectively of the aglycone. The sulphate, without further purification, was treated in aqueous suspension with excess of ammonia at 100° for 4 hours and yielded the crude aglycone, m. p. 219—220°, as expected. On crystallisation from 80% alcohol (charcoal), however, the m. p. dropped to 184—186°. The m. p. was only slowly raised by recrystallisation but after a very lengthy series of crystallisations from 80% alcohol, 80% methyl alcohol, 80% dioxan and finally from methyl alcohol two products were obtained, one, m. p. 199·5—202°, unchanged on further crystallisation, and the other, m. p. 213—217°, in much smaller yield. Probably the purification is retarded also by the presence of solasodiene and the corresponding compound from solauricidine formed as by-products (see Part II).

If the crude hydrochloride obtained by hydrolysis of the glycoalkaloid is purified by repeated crystallisation from 80% alcohol to m. p. 316° (decomp.) and then converted into the aglycone, solasodine, m. p. 198—200°, is obtained without difficulty.

The purified hydrochloride, sulphate, nitrite and the acetyl derivative of this material, m. p. 198—200°, all had the same m. p.'s as those prepared from authentic solasodine and respective pairs showed no depression.

The following crystallographic measurements were made in 1938 by Dr. F. J. Turner, using a microscope fitted with a universal stage.

Solasodine (*ex S. aviculare*; see Part I):

$2V$ = 70°, 74°, 76° (mean 74° ± 2°). Optical sign positive. Six-sided crystals with γ perpendicular to the plane of flattening (Fig. 1). θ = 107° ± 3°.

Solauricidine:

$2V$ = 54°, 56°, 58°, 58° (mean 56° ± 2°). Optical sign positive. Small, ill-defined, platy crystals with γ approximately perpendicular to the plane of flattening.

The following measurements were made by Dr. F. J. Turner in 1940 on the purest specimens available, which were all crystallised from the same sample of methyl alcohol before measurement.

Solasodine (*ex S. sodomæum*), m. p. 199—202° :

$2V = 73°, 73°, 74°, 72°, 74°$ (mean $73° \pm 1°$). Optical sign positive; all homogeneous crystals (Fig. 1). $\theta = 112° \pm 1°$, $\phi = 124° \pm 1°$.

Solauricidine (*ex S. auriculatum*), m. p. 220—223° (obtained from the original alcoholic extraction process) :

$2V = 74°, 78°, 65°, 78°, 72°, 70°, 68°, 75°, 72°, 77°, 80°$ (mean 73·5°) Optical sign positive. Refractive indices : α 1·53 ~ 1·54, β 1·55 ~ 1·56.

Some of the crystals were clear and homogeneous, but many had central, apparently fibrous cores, surrounded by a clear border zone (Fig. 2).

The optic orientations of the central and the border zone do not coincide, but in both zones the axial angle = $74° \pm 2°$. This may simply be a result of the way in which the substance was crystallised, perhaps twinning or probably large crystals have grown around nuclei consisting of tufts of fibres that had first crystallised.

FIG. 2.

FIG. 1.

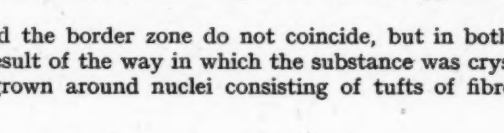

FIG. 3.

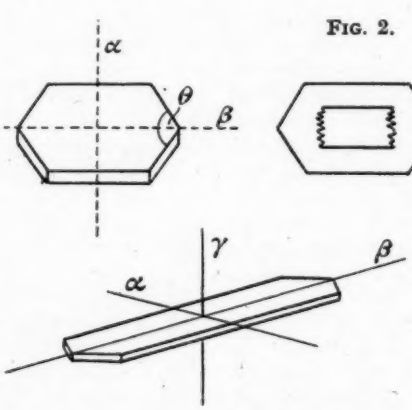

FIG. 4.

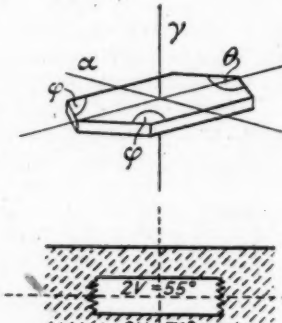

FIG. 5.

Solasodine (*ex S. auriculatum*), m. p. 199·5—202° :

$2V = 74°, 70°, 73°, 68°, 74°, 70°, 75°, 73°, 75°, 75°, 75°, 74°, 73°, 78°, 74°, 74°$ (mean 73·5°). Optical sign positive. Clear homogeneous crystals. Refractive indices : α 1·53 ~ 1·54, β 1·55 ~ 1·56.

The specimens of solasodine (*ex S. auriculatum*) and solauricidine are all closely similar in crystal habit, crystallographic angles, optic orientation, and, in so far as they have been measured, in refractive index. The crystals are tabular in habit, being flattened perpendicularly to the acute bisectrix (γ) and somewhat elongated (sometimes much elongated) parallel to β (Figs. 3 and 4). $\phi = 125° \pm 3—4°$, $\theta = 110° \pm 3—4°$.

Many crystals show traces of cleavage parallel or subparallel to the plane $\beta\gamma$ or at least parallel to β.

All three samples were then recrystallised from methyl alcohol by Mr. N. E. Stace, M.Sc., at Otago University and resubmitted for crystallographic measurement, with the following results.

Solasodine (*ex S. sodomæum*) :

$2V = 54°, 55°, 53°, 54°$ (mean 54°). Optical sign positive. Crystal angles the same as before crystallisation. Small clear crystals, readily measured.

Solauricidine (*ex S. auriculatum*) :

$2V = 59°, 59°, 54°, 52°, 62°, 60°, 59°, 58°$ (mean 58°). Optical sign positive.

Solasodine (*ex S. auriculatum*) :

$2V = 54°, 55°, 54°, 56°, 54°, 55°, 54°$ (mean 54°). Optical sign positive. Clear, tabular, homogeneous crystals. One crystal had $2V = 76°$, and another had a central zone, $2V = 55°$, surrounded by an outer zone, $2V = 76°$, the two being in the same optic orientation (Fig. 5). In the latter crystal there appears to be a parallel growth of two separate identities.

The hydrochloride of solauricidine gave the following values, indistinguishable from those of solasodine hydrochloride (see Part I) :

$2V = 78°, 80°, 80°, 88°, 90°$ (mean $85° \pm 5°$). Optical sign positive. Six-sided tabular crystals with γ inclined at 60—70° (approximate value only) to the plane of flattening and slightly elongated parallel to β in most cases. The hydrochloride has the same orientation and habits as solasodine hydrochloride, *ex S. sodomæum* or *ex S. aviculare*.

All the above optic axial angles were measured on separate crystals.

We are indebted to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for grants, to Mesrs. Hughes and Cossar, Ltd., Auckland, for the loan of a press, to Miss M. P. Bartrum, M.Sc., for the purification of some of the material, and one of us (R. C. B.) acknowledges the award of a Sir George Grey Scholarship.

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4. Solanum *Alkaloids. Part IV. The Glycosidic Moiety of Solauricine.*

By Lindsay H. Briggs and John J. Carroll.

The glycosidic moiety of solauricine is shown to consist of glucose, rhamnose, and galactose. The trisaccharide portion of the molecule is therefore probably the same as that occurring in solanine and solasonine.

In Part III (preceding paper) evidence has been given that the glucosidic alkaloid solauricine isolated from *Solanum auriculatum* and its aglycone, solauricidine, are isomeric with but different from the corresponding bases solasonine and solasodine from *S. sodomæum*. The possibility that the aglycone solauricidine is combined in the glucosidic alkaloid with a trisaccharide different from that occurring in both solanine and solasonine (Zemplén and Gerecs, *Ber.*, 1928, **61**, 2294; Oddo and Caronna, *ibid.*, 1934, **67**, 444; cf. also Part II, this vol., p. 3) has been tested experimentally and in the sugar solution obtained on hydrolysis the presence of galactose, rhamnose, and glucose has been established. The galactose was identified as its *o*-tolylhydrazone by treatment with *o*-tolylhydrazine, which does not yield a solid derivative with glucose or rhamnose (van der Haar, *Rec. Trav. chim.*, 1917, **37**, 108).

Treatment of the sugar solution with phenylhydrazine gave a mixture of osazones from which glucosazone was isolated by fractional crystallisation, and after evaporation of another portion almost to dryness, followed by treatment with absolute alcohol, rhamnose separated in a pure form and was identified as its *p*-nitrophenylhydrazone. The deposition of rhamnose from the sugar solution before glucose or galactose agrees with the experiments of Zeisel and Wittmann (*Ber.*, 1903, **36**, 3554), but according to Hudson and Tanovsky (*J. Amer. Chem. Soc.*, 1917, **39**, 1013) rhamnose is much more soluble than either glucose or galactose in aqueous alcoholic solution.

Since these sugars from solauricine also form the trisaccharide moiety of solanine and solasonine, on phytochemical grounds all three trisaccharides are probably identical. Zemplén and Gerecs do not indicate whether glucosidic or ether linkages are present in the sugars, but Oddo and Caronna suggest the following general formula for solanine:

$$\underset{\text{Rhamnose}}{C_6H_{11}O_4}—O—\underset{\text{Galactose}}{C_6H_{10}O_4}—O—\underset{\text{Glucose}}{C_6H_{10}O_4}—O—\underset{\text{Solanidine}}{\text{base}}$$

and an unusual type of linkage for solasonine (cf. also Oddo and Cesaris, *Gazzetta*, 1914, **44**, ii, 182)

$$\text{Base}—O—\underset{\text{Glucose}}{\underset{\displaystyle[CH\cdot OH]_4}{\underset{CH_2\cdot OH}{CH}}}—O—\underset{\text{Galactose}}{\underset{\displaystyle[CH\cdot OH]_4}{\underset{CH_2\cdot OH}{CH}}}—O—\underset{\text{Rhamnose}}{\underset{\displaystyle[CH\cdot OH]_4}{\underset{CH_3}{CH}}}—O—\text{base}$$

or $$\text{base}—O—C_6H_{12}O_5—O—C_6H_{12}O_5—O—C_6H_{12}O_4—O—\text{base}$$

Apart from the fact that it has been shown in Part II that only one molecule of solasodine is joined to the trisaccharide and not two as suggested by Oddo, by comparison of the above formulæ it is seen that the sugar units of solasonine contain one molecule of water more than the corresponding sugars in solanine. Since a trisaccharide containing glucose, galactose, and rhamnose units does not occur to the authors' knowledge elsewhere in the plant kingdom other than in the *Solanum* genus, it seems most unlikely that the sugar units in solanine and solasonine differ in the way indicated by Oddo and co-workers. The partial formula given for solanine agrees for normal pyranose (or furanose) structures for each sugar unit, so solasonine and solauricine should be similarly formulated. Oddo and Cesaris (*loc. cit.*) have reported that solasonine fails to react with phenylhydrazine and it can thus be concluded that the sugars are united to each other through their potential aldehyde structures.

On the above formulation both solanine and solasonine should yield an acetate containing nine acetyl groups (all combined with sugar hydroxyl groups). This is not, however, in accordance with the results of previous workers on both solanine (Hilger, *Annalen*, 1879, **195**, 321; Heiduschka and Sieger, *Arch. Pharm.*, 1917, **255**, 18; Zemplén and Gerecs, *loc. cit.*; Oddo and Caronna, *loc. cit.*; Heiduschka and Philippi, *Ber.*, 1935, **68**, 669) and solasonine (Oddo and Caronna, *loc. cit.*).

Since these previous results, however, are not concordant in themselves, our conclusions for the formulation of the trisaccharide moiety are not thereby invalidated.

Experimental.

Solauricine, m. p. 270—271° (decomp.), was obtained by working up the alcoholic extract of the dried green berries of *S. auriculatum* as described in Parts I and III.

Solauricine (20 g.) was hydrolysed by heating with 2% sulphuric acid (4 c.c. of concentrated acid in 400 c.c. of water) on the water-bath for 3 hours. After cooling, the precipitate of solauricidine sulphate was removed, and the filtrate heated for 2 hours to complete the hydrolysis and again filtered. The sulphate, when treated in aqueous suspension with ammonia, afforded material, m. p. 218—220°, which after repeated crystallisation from 80% alcohol (charcoal) formed colourless plates of solauricidine, m. p. 219°.

The combined filtrates from the hydrolysis were shaken with excess of barium carbonate and kept for 24 hours, and the insoluble material removed. The neutral filtrate was concentrated in a vacuum to a fifth of its volume with the use of an anti-foaming device. After filtration from a small amount of solid matter a clear, almost colourless solution of the sugars was obtained.

Identification of Galactose.—An aliquot portion (13·5 c.c.) of the sugar solution was mixed with freshly distilled *o*-tolylhydrazine (0·61 g.) and dissolved in the minimum amount of alcohol. After ½ hour's heating at 100° and cooling, colourless needles formed, which were collected and washed with 50% alcohol. The crystals then had m. p. 173° (decomp.), undepressed by authentic galactose-*o*-tolylhydrazone prepared in a similar manner. Van der Haar (*loc. cit.*) gives m. p. 176° (decomp.).

Identification of Rhamnose.—An aliquot portion of the sugar solution (13·5 c.c.) was evaporated almost to dryness on a water-bath, triturated with absolute alcohol, and kept for some days. Large, colourless, homogeneous crystals had then separated which, after being washed with 50% alcohol and dried, had m. p. 90—91°, undepressed by a commercial sample of rhamnose of the same m. p.

The above material (100 mg.), m. p. 90—91°, and *p*-nitrophenylhydrazine (100 mg.) were dissolved in alcohol (15—20 c.c.), boiled for a few minutes, and allowed to cool. The yellow needles which separated, after being washed with 50% alcohol and dried, had m. p. 191°, undepressed by authentic rhamnose-*p*-nitrophenylhydrazone similarly prepared. Butler and Cretcher (*J. Amer. Chem. Soc.*, **1931**, **53**, 4363) record m. p. 190—191°.

Identification of Glucose.—A further portion of the original sugar solution (15 c.c.) was heated with freshly distilled phenylhydrazine (4·85 g.), glacial acetic acid (7·5 c.c.), and water (30 c.c.) on the water-bath for ½ hour; more water (2 c.c.) was then added, and heating continued for ½ hour. During the first heating and afterwards the characteristic sheaf-like needles of glucosazone could be detected in the reaction mixture. The product, after being washed with 2% acetic acid, had m. p. 176—187° (decomp.), but after successive trituration with ether, acetone and boiling acetone the m. p. rose to 197—199° (decomp.). The crystals were then dissolved in a large quantity of boiling acetone, and the solution concentrated to half volume and allowed to cool. Glucosazone separated, m. p. 209—209·5°, undepressed by an authentic specimen.

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5. *Reactions of (+)- and (−)-γ-Methyl-α-ethylallyl Alcohols and their Derivatives.*

By RAYMOND S. AIRS, MICHAEL P. BALFE, and JOSEPH KENYON.

From a study of the mutarotation of γ-methyl-α-ethylallyl alcohol it is concluded that there is a steady transformation by anionotropic change into α-methyl-γ-ethylallyl alcohol, the sign of rotation of the isomeric alcohol produced being similar to that of the original alcohol. Evidence from parachors suggests some peculiarity of structure in the allylic alcohols, and a pseudo-cyclic configuration is proposed which is in harmony with the retention of asymmetry on anionotropic change. The chloride of γ-methyl-α-ethylallyl alcohol gives a mixture of γ-methyl-α-ethylallyl and α-methyl-γ-ethylallyl alcohols on hydrolysis, mainly *via* dissociation with extensive racemisation.

A method for analysis of mixtures of optically active methyl-*n*-butyl- and ethyl-*n*-propyl-carbinols is introduced, which may be applicable to mixtures of other optically active substances.

THE acid phthalic *ester* of γ-methyl-α-ethylallyl alcohol can be separated, by fractional crystallisation of its brucine salt, into (+)- and (−)-forms. Table I gives the rotatory powers of the (+)-phthalate in various solvents; the characteristic diagram (Lowry, "Optical Rotatory Power," 1935, p. 418) plotted from these data indicates slightly complex dispersion. The (+)- and the (−)-γ-methyl-α-ethylallyl alcohol are obtained from these esters by saponification with 5N-sodium hydroxide. As with other αγ-disubstituted allyl alcohols, partial racemisation occurs if more dilute alkali is used (Balfe and Kenyon, *Nature*, **1941**, **148**, 196). Table II gives the rotatory powers of the (+)-alcohol at different temperatures in the homogeneous state. The observations at 15° fit a one-term Drude equation $[\alpha]_4^{15°} = 3{\cdot}78(\lambda^2 - 0{\cdot}0638)$, which has a characteristic frequency of 2525 A. This is close to the characteristic frequency, 2690 A., found for γ-methyl-α-*n*-propylallyl alcohol by Arcus and Kenyon (J., 1938, 312) who, nevertheless, from other evidence, concluded that the dispersion was not truly simple. In view

TABLE I.

Specific rotatory powers of (+)-γ-methyl-α-ethylallyl hydrogen phthalate in various solvents.

Solvent.	*c.*	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.	$[\alpha]_{4358}$.	Solvent.	*c.*	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.	$[\alpha]_{4358}$.
H_2O *	10·0	+20·2°	+21·7°	+26·0°	+60·3°	C_5H_5N	10·0	+18·1°	+19·7°	+22·5°	+46·0°
	5·0	20·7	22·0	26·5	60·1		5·0	17·8	19·0	22·1	48·0
	2·5	20·0	21·1	23·9	56·4		2·5	17·4	18·8	20·8	49·0
EtOH	10·0	26·6	27·8	32·5	65·7	C_6H_6	5·0	10·6	11·0	12·9	27·4
	5·0	27·5	28·8	33·4	68·5	$CHCl_3$	5·0	11·5	13·0	15·0	32·9
	2·5	27·2	29·7	32·5	68·0	CS_2	10·0	−12·4	−13·0	−14·5	−24·7
$CH_3{\cdot}NO_2$	10·0	18·8	20·3	23·3	48·5		5·0	13·9	14·5	16·1	28·2
	5·0	21·4	22·8	26·2	53·0		2·5	14·4	14·8	16·2	27·8
	2·5	23·6	24·4	29·0	60·0						

* The sodium salt of the acid ester was used in this solvent.

TABLE II.

Influence of temperature on the rotatory power of (+)-γ-methyl-α-ethylallyl alcohol (in the homogeneous state; $l = 0{\cdot}5$).

Temp.	d_4^t.	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.	$[\alpha]_{4358}$.	Temp.	d_4^t.	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.	$[\alpha]_{4358}$.
15°	0·8431	+13·5°	+14·1°	+16·1°	+29·9°	40°	0·8218	+11·4°	+12·0°	+13·7°	+25·5°
20	0·8389	13·1	13·7	15·7	29·0	50	0·8131	10·5	11·1	12·7	23·8
30	0·8303	12·2	12·8	14·7	27·3	60	0·8047	9·7	10·2	11·8	22·1

of their unsaturation, it is probable that extension of the observations for both alcohols to shorter wave-lengths would show the necessity for a second term in the equations, as is indicated by the observations of Levene and Haller (*J. Chem. Physics*, 1937, **5**, 980), who found that two-term equations were required to fit the rotatory dispersion of αγ-dimethylallyl alcohol and other unsaturated secondary alcohols.

Reduction of the (+)-alcohol with hydrogen gives (+)-ethyl-*n*-propylcarbinol, which has $[\alpha]_{5893}^{20°}$ + 7·09° (homogeneous) and gives a hydrogen phthalate having $[\alpha]_{5893}^{20°}$ + 9·70° in chloroform solution. The maximum values given by Kenyon (J., 1914, **105**, 2226) are, for the (−)-carbinol $[\alpha]_{5893}^{20°}$ − 4·21°, and for its phthalate, $[\alpha]_{5893}^{20°}$ − 5·76°. The ratio between the rotation of the carbinol and that of the phthalate is the same (1·37) in both sets of results, indicating that the higher values now found are not due to impurity, and we are of the opinion that the (+)-carbinol and its ester are optically pure.

(−)-γ-Methyl-α-ethylallyl hydrogen phthalate (having 40% of the maximum rotatory power) reacts with methyl alcohol to afford a *methyl hexenyl ether* of $\alpha_{5461}^{21°}$ − 0·18° (*l*, 0·5). From the alcohol obtained from the same specimen of phthalate, by a reaction which does not disturb the bonds of the asymmetric carbon atom (reaction of the potassium derivative of the alcohol with methyl iodide), methyl γ-methyl-α-ethylallyl ether is obtained with $\alpha_{5461}^{23°}$ + 6·88° (*l*, 0·5). This result affords further evidence of the extensive racemisation which occurs in replacement reactions of derivatives of the αγ-disubstituted allyl alcohols (Arcus and Kenyon, J., 1938, 1912; Balfe and Kenyon, *loc. cit.*). Rearrangement may also have occurred during the replacement reaction, but practical difficulties prevented its detection.

(+)- and (−)-γ-Methyl-α-ethylallyl alcohols undergo mutarotation at rates varying with different specimens (Table III). The rate is increased by addition of a trace of acid, and since old specimens were found to have become acid, variations in the amount of acid formed may account for the variations in rates of mutarotation. The mutarotation is not due to simple racemisation, since the rotatory power of the hexanol obtained by reduction of the alcohol after mutarotation is higher than would be expected if racemisation alone had occurred. The hydrogen phthalate of this hexanol has, in fact, a specific rotation higher than that of optically pure ethyl-*n*-propylcarbinyl hydrogen phthalate. The mutarotation is probably attributable to an anionotropic rearrangement, with formation of α-methyl-γ-ethylallyl alcohol, since by fractional crystallisation of the p-*xenylurethane* of a 2-years old specimen of γ-methyl-α-ethylallyl alcohol, the urethane of the α-methyl-γ-ethylallyl isomeride was obtained. Confirmatory evidence of the rearrangement is given by the density of the hexanol formed by reduction of γ-methyl-α-ethylallyl alcohol. During storage of the unsaturated alcohol the density of its reduction product—prepared after different intervals—gradually alters from that of ethyl-*n*-propylcarbinol to a value intermediate between those of ethyl-*n*-propyl- and methyl-*n*-butyl-carbinols.

The ratio between the specific rotation of (+)-ethyl-*n*-propylcarbinyl hydrogen phthalate (in chloroform solution) and the observed rotation of the (+)-carbinol (homogeneous; *l*, 1) at λ_{5893} is 1·7. For methyl-*n*-butylcarbinol the corresponding ratio is 4·6. On account of the difference between these two ratios it becomes possible to deduce the proportions of the different optically active species present in a mixture of ethyl-*n*-propyl- and methyl-*n*-butyl-carbinols by observing the rotatory power of the mixture and

TABLE III.

Mutarotation of γ-methyl-α-ethylallyl alcohol (transferred at intervals from stoppered bottles to a 0·5-dm. polarimeter tube).

(i) Specimen of (+)-γ-methyl-α-ethylallyl alcohol.

Time, days.	*t*.	α_{5893}.	α_{5780}.	α_{5461}.	α_{4358}.	$\alpha^{20°}_{5461}$ (calc.).
0	21·0°	+4·87°	+5·12°	+5·94°	+11·15°	+5·97°
1	21·0	4·93	—	5·97	11·09	5·98
3	19·0	5·00	5·26	6·12	11·28	6·09
6	19·0	5·03	5·25	6·06	11·23	6·03
8	21·0	—	5·12	5·94	—	5·96
22	18·0	5·05	—	6·21	11·41	6·14
24	18·0	5·04	—	6·16	11·46	6·10
42	19·5	4·98	—	6·05	11·04	6·05
59	19·5	4·92	5·22	6·00	11·05	6·00
119	27·5	4·04	4·26	4·96	9·26	5·14
122	19·0	—	4·56	5·26	9·85	5·23
125	20·0	—	4·51	5·14	9·64	5·14
129	24·0	4·21	4·47	5·13	9·50	5·23
132	23·5	—	4·30	4·89	9·30	4·97
134	22·0	—	4·31	4·95	9·33	5·00
136	22·0	4·05	4·30	4·95	9·30	5·00
174	18·3	4·00	4·15	4·75	9·06	4·70
188	19·0	3·86	4·01	4·64	8·70	4·62
198	20·0	3·86	4·04	4·64	8·66	4·64
223	20·0	—	4·01	4·69	8·50	4·69
370	19·0	3·66	3·94	4·50	8·40	4·47
594	18·5	3·53	3·77	4·32	8·00	4·29
987	19·0	3·35	3·55	4·07	7·58	4·05
1156	21·5	3·33	3·41	4·04	7·49	4·06

(ii) Specimen of (−)-γ-methyl-α-ethylallyl alcohol.

Time, days.	*t*.	α_{5893}.	α_{5780}.	α_{5461}.	α_{4358}.	Time, days.	*t*.	α_{5893}.	α_{5780}.	α_{5461}.	α_{4358}.
0	19·5°	−4·98°	−5·19°	−5·95°	−10·95°	919	19·0°	−4·90°	—	−5·96°	−10·88°
300	19·5	4·99	5·23	5·98	10·50	1634	21·0	4·90	−5·20°	5·90	11·10
524	17·5	4·94	5·22	5·97	11·05						

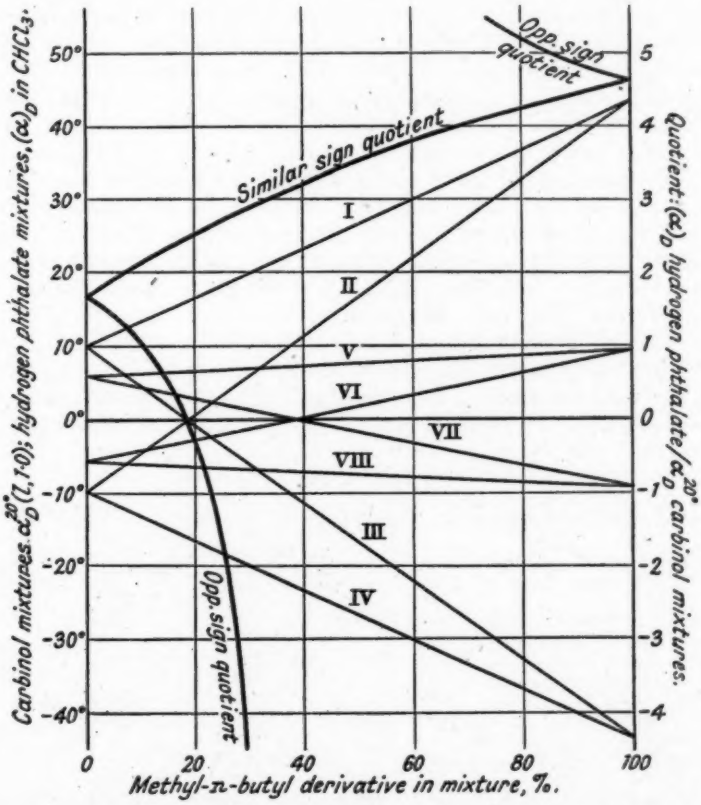
(iii) Specimen of (+)-γ-methyl-α-ethylallyl alcohol.

0	20·5	+5·40	+5·75	+6·66	+12·20		(1% Formic acid added.)				
736	21·0	5·36	5·60	6·50	11·85	757	20·0	+5·16	+5·25	+6·15	+11·15

of the mixture of hydrogen phthalic esters prepared from it. (The method may be applicable to the analysis of mixtures of other optically active compounds, and its application might be extended by the use of physical properties other than optical rotatory power.) If the mixture of hexanols has been obtained by reducing a mixture of γ-methyl-α-ethylallyl and α-methyl-γ-ethylallyl alcohols, the results of the calculation can be used to deduce the composition of the mixture of hexenols. In applying this procedure two assumptions are made, *viz.*, that the specific rotation of each phthalate or of each alcohol is not altered by dilution with its isomeride, and that significant amounts of other optically active substances are not present in the mixture of alcohols. The method is best illustrated by an example.

In the figure the observed rotatory powers (l, 1; λ_{5893}) of mixtures of (+)- and (−)-ethyl-*n*-propyl- and -methyl-*n*-butyl-carbinols and the specific rotations (in chloroform) of their hydrogen phthalates are plotted against the composition of the mixture, giving straight lines. The curve shows how the ratio of specific rotation of phthalate mixture to rotation of carbinol mixture varies according to the composition of the mixture. The data for methyl-*n*-butylcarbinol and its hydrogen phthalate are taken from the results of Pickard and Kenyon (J., 1911, **99**, 45), and those for ethyl-*n*-propylcarbinol and its ester were determined with material obtained by reduction of freshly prepared (+)-γ-methyl-α-ethylallyl alcohol. The first specimen of this alcohol referred to in Table III was reduced to hexanol after the last observation of rotatory power quoted (1156 days) had been made. The hexanol had $\alpha^{20°}_{5893}$ + 5·0° (l, 1·0) and its hydrogen phthalate had $[\alpha]^{20°}_{5893}$ + 16·7° in chloroform solution. The ratio between these two rotations is 3·34 which, according to the curve in the figure, corresponds to a mixture of 56% of ethyl-*n*-propyl- and 44% of methyl-*n*-butyl-carbinol, both of the same sign and therefore both dextrorotatory, since the mixture is dextrorotatory. Now a mixture of the optically pure (+)-carbinols in this proportion would have $\alpha^{20°}_{5893}$ + 7·4° (l, 1·0). The observed rotatory power, + 5·0°, thus shows that the optically active carbinols make up 67·5% of the mixture. The composition of the mixture is therefore 37·8% of (+)-ethyl-*n*-propyl, 29·7% of (+)-methyl-*n*-butyl-carbinol, and 32·5% of optically inactive material, presumably a mixture of both carbinols.

(+)-Ethyl-*n*-propylcarbinol is related in configuration to (+)-γ-methyl-α-ethylallyl alcohol, from which it is obtained by reduction, a process which cannot cause change in configuration. The relation between sign of rotation and configuration of methyl-*n*-butylcarbinol and α-methyl-γ-ethylallyl alcohol has not been directly determined, but it can be deduced that in this case also similar signs of rotation indicate similar configurations. The α-methyl-γ-ethylallyl alcohol formed during the mutarotation of (+)-γ-methyl-α-ethylallyl alcohol must be dextrorotatory because the dispersion ratio ($\alpha_{4358}/\alpha_{5893}$) does not alter during the process of mutarotation; formation of the (−)-tautomeride would cause the rotatory dispersion of the mixture to become complex (or anomalous) and so alter the dispersion ratio. This (+)-α-methyl-γ-ethylallyl alcohol gives, on reduction, (+)-methyl-*n*-butylcarbinol, as shown above.



I. *Hydrogen phthalates of* d-*methyl*-n-*butyl- and* d-*ethyl*-n-*propyl-carbinols.*
II. ,, ,, d- ,, ,, l- ,, ,, ,,
III. ,, ,, l- ,, ,, d- ,, ,, ,,
IV. ,, ,, l- ,, ,, l- ,, ,, ,,
V. d-*Methyl*-n-*butyl- and* d-*ethyl*-n-*propyl-carbinols.*
VI. d- ,, ,, l- ,, ,, ,,
VII. l- ,, ,, d- ,, ,, ,,
VIII. l- ,, ,, l- ,, ,, ,,

***Optical rotatory powers** of mixtures of ethyl-n-propyl- and methyl-n-butyl-carbinols and of mixtures of their hydrogen phthalates; also ratios of rotations to those of carbinol mixtures.*

The results previously calculated can now be applied to ascertain the composition of the mixture formed during the mutarotation of (+)-γ-methyl-α-ethylallyl alcohol, a correction being applied for the fact that the alcohol used in this experiment had only 92·5% of the maximum rotatory power. The final calculation shows that during the mutarotation (1156 days) racemisation occurred to the extent of 27%, 41% of (+)-γ-methyl-α-ethylallyl alcohol remained, and 32% of (+)-α-methyl-γ-ethylallyl alcohol was formed. Although the racemic portion of the product probably contains both isomerides, the noteworthy feature of the result is the very high retention of optical activity, even if the rearrangement is irreversible; if it involves a state of equilibrium, the retention of optical activity becomes still more remarkable. There is some evidence that the rearrangement is reversible. Although it results in an

eventual decrease in rotatory power, in the initial stages the rotatory power rises [see section (i), Table III]. The most likely explanation for this is that the rearrangement occurs to a preponderating extent with retention of optical activity, but that it is reversible, and is accompanied by a certain amount of racemisation. On this basis, the initial rise in rotatory power would be ascribed to conversion of (+)-γ-methyl-α-ethyl- into (+)-α-methyl-γ-ethyl-allyl alcohol; the rate of increase is diminished as equilibrium is approached, and a decrease sets in when the irreversible loss of rotatory power, due to racemisation, becomes appreciable.*

Kenyon, Partridge, and Phillips (J., 1937, 207) suggested a cyclic configuration in order to explain the retention of optical activity during the anionotropic conversion of (−)-α-phenyl-γ-methylallyl hydrogen phthalate into the (+)-γ-phenyl-α-methylallyl ester. This suggestion can be extended to cover the present observations. The notion of such a cyclic configuration for the substituted allyl alcohols recalls the cyclic structure for αγ-dimethylallyl alcohol discussed by Hills, Kenyon, and Phillips (J., 1936, 576) as a result of parachor determinations. We have therefore re-examined the question of the parachors of the substituted allyl alcohols. The parachor of γ-methyl-α-ethylallyl alcohol is 267·2, different specimens, when pure, all giving values within 0·3 unit of this. Hills, Kenyon, and Phillips (*loc. cit.*) recorded the parachor of αγ-dimethylallyl alcohol as varying between 226 and 233, but we find the freshly purified alcohol to have a parachor of 230·2 and again ascribe variations to the presence of impurity; *e.g.*, after 6 months' storage the parachor changes to 228·8. Hills, Kenyon, and Phillips (*loc. cit.*) give the parachor of allyl alcohol as 159, in close agreement with the value calculated from Sugden's constants ("Parachor and Valency," 1930). We now find, however, a value of 153·9 for allyl alcohol and consider that the higher figure previously recorded was due to incomplete drying of the material, a difficult process for this alcohol (Tornoe, *Ber.*, 1891, **24**, 2670).

Table IV summarises the results of the parachor determinations. Allyl alcohol and two α-substituted, one γ-substituted, and five αγ-disubstituted allyl alcohols, as well as methyl-β-methylallylcarbinol, all have parachors below the values calculated from Sugden's constants (*op. cit.*) and, with the exception of allyl alcohol, below those calculated from Mumford and Phillips's constants (J., 1929, 2113). A low

TABLE IV.

Parachors of unsaturated alcohols and their esters, and of saturated alcohols.

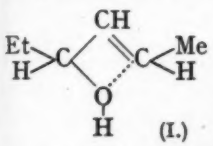
Substance.	Observed [*P*]. 15°.	20°.	40°.	Observed $[P]_{40°} - [P]_{15°}$.	Calc. [*P*] (Sugden).
Unsaturated.					
Allyl alcohol [1]	153·9	—	154·2	0·3	160·2
α-Ethylallyl alcohol [2]	—	228·1	—	—	238·2
α-*n*-Butylallyl alcohol [2]	—	305·9	—	—	316·2
γ-Phenylallyl alcohol [2]	—	324·4	—	—	331·2
αγ-Dimethylallyl alcohol [1]	230·2	—	230·4	0·2	238·2
γ-Methyl-α-ethylallyl alcohol [1]	267·2	—	267·5	0·3	277·2
α-Phenyl-γ-methylallyl alcohol [3]	—	360·6	—	—	372·1
γ-Phenyl-α-methylallyl alcohol [3]	—	367·4	—	—	372·1
γ-Methyl-α-allylallyl alcohol [1]	295·4	—	295·9	0·5	301·8
Methyl-β-methylallylcarbinol [1]	268·4	—	268·6	0·2	277·2
Allyl acetate [1]	245·1	—	245·3	0·2	244·0
γ-Methyl-α-ethylallyl acetate [1]	362·1	—	361·5	0·4	361·0
γ-Methyl-α-ethylallyl benzoate [1]	490·2	—	490·5	0·3	494·9
Saturated.					
Methyl alcohol [4]	88·2	88·3	88·7	0·5	93·2
Ethyl alcohol [4]	126·8	126·9	127·5	0·7	132·2
n-Amyl alcohol [1]	241·2	—	242·4	1·2	249·2

[1] Determinations made in present work. [2] Hills, Kenyon, and Phillips (*loc. cit.*). [3] Kenyon, Partridge, and Phillips (*loc. cit.*). [4] From data given by Sugden (*op. cit.*). Values at 15° and 40° interpolated.

parachor value is not, however, peculiar to unsaturated alcohols, for it is shown also by saturated alcohols, and in this case is ascribed to association (Sugden, *op. cit.*). Hills, Kenyon, and Phillips concluded that the low parachor of the unsaturated alcohols was not due to association, because they found the parachor of allyl alcohol to be normal, and although this evidence was unsatisfactory, we consider, for the following reason, that their conclusion was justified. The parachors of saturated alcohols increase with rise of temperature, as is to be expected if the parachor anomaly is due to

* This argument assumes that (+)-α-methyl-γ-ethylallyl alcohol has a higher specific rotatory power than the isomeric alcohol. The rotatory power of the former is apparently not on record and we have not had an opportunity to determine it or to measure the rate at which the rearrangement proceeds—a desirable datum.

association (Sugden, *op. cit.*). The amount of this increase varies with the molecular weight of the alcohol; Owen, Quale, and Beavers (*J. Amer. Chem. Soc.*, 1939, **61**, 900) find that the parachors of saturated tertiary alcohols increase by about 0·2% for every 10° rise in temperature, and a similar increase is shown by the three saturated *n*-alcohols given in Table IV. The parachors of unsaturated alcohols also increase with rise of temperature, but to a much less extent than those of saturated alcohols and independently of the variation in molecular weight. For example, the parachor of *n*-amyl alcohol (*M*, 88) increases by 1·2 units between 15° and 40°, whereas that of αγ-dimethylallyl alcohol (*M*, 86) increases by only 0·2 unit in the same temperature range. The low parachors of allyl alcohol and its α- and γ-substituted derivatives are therefore unlikely to be due to association, and we regard them as evidence of some structural peculiarity in the alcohols. The assumption that this peculiarity involves some form of co-ordination between the hydroxyl group and the C_γ atom brings the parachor observations into line with the phenomena associated with the mutarotation of γ-methyl-α-ethylallyl alcohol, and such an intramolecular association may be expected to be affected by temperature to a lesser extent than the intermolecular association of saturated alcohols. Hills, Kenyon, and Phillips (*loc. cit.*) considered the possibility that the substituted allyl alcohols were equilibrium mixtures of open-chain and cyclic (propylene oxide) tautomerides. Raman-spectra observations (Dupont *et al.*, *Bull. Soc. chim.*, 1939, **5**, 1208, 1215) on a substituted allyl alcohol indicate that the molecule is unsaturated, and the molecular refractivities of a number of such alcohols (Arcus and Kenyon, J., 1938, 312) suggest that the cyclic structure can only be present in a very small proportion of molecules, if any. Accordingly, we propose for γ-methyl-α-ethylallyl alcohol a structure which can be represented as (I). Against the possibility of a cyclic structure for αγ-dimethylallyl alcohol, Hills, Kenyon, and Phillips (*loc. cit.*) argued that, as a result of *cis–trans*-isomerisation, two stereochemical modifications of structure about the C_γ atom should exist, a possibility which was inconsistent with certain of their observations. This argument does not hold against the suggestion now put forward, since the mutarotation experiments described above show that one of the stereoisomeric modifications of the C_γ atom is formed to a preponderating extent.



(I.)

The essential feature of the formulation (I) is that it implies some form of attraction (or interaction) between the oxygen atom and the γ-carbon atom, in spite of the fact that the distance between these two atoms is greater than the carbon–oxygen covalent length. This attraction, it is suggested, alters the molecular volume of the alcohol, and holds the oxygen atom in such a position that, when rearrangement occurs, one of the two possible stereoisomeric forms of the new asymmetric carbon atom is formed to a greater extent than the other. In the esters of the substituted allyl alcohols, there may be a similar attraction between the doubly-bonded oxygen of the esterified carboxyl group and the γ-carbon atom. This would explain the retention of asymmetry during the anionotropic rearrangement of certain of these esters (Balfe and Kenyon, *Trans. Faraday Soc.*, in press), but in this case there is no need to assume any modification of molecular volume, because the normal interatomic dimensions, in a six-membered pseudo-cyclic configuration, bring the two atoms in question into proximity. Hence, no parachor anomaly is found in the esters. Hills, Kenyon, and Phillips record the parachors of five esters, three ethers, and the chloride of αγ-dimethylallyl alcohol; with one exception, which they ascribe to impurity, these compounds have values close to those calculated from Sugden's constants. Similarly, Table IV shows that *γ-methyl-α-ethylallyl acetate* and *benzoate* and allyl acetate have parachors close to the calculated values.

γ-Methyl-α-ethylallyl alcohol is converted into the *chloride* by the action of thionyl chloride and quinoline, the (+)-alcohol giving a (−)-chloride. The optically active chloride exhibits slightly complex dispersion in the visible spectrum. Different specimens of the chloride varied in rotatory power, suggesting the occurrence of some racemisation during its preparation, but in all cases the rotatory power was comparatively high, rendering extensive racemisation improbable. The chloride is chemically unstable (it evolves hydrogen chloride after a few days) and for this reason observations of its mutarotation were not undertaken; all experiments were done with freshly prepared chloride.

The chloride is hydrolysed by water in the presence of calcium carbonate. It is less easily hydrolysed than the chloride of αγ-dimethylallyl alcohol and more easily than that of γ-methyl-α-*n*-propylallyl alcohol. Hydrolysis of the (−)-chloride gives a hexenol of very low lævorotation; this, on reduction, gives a slightly dextrorotatory hexanol which is optically inactive at λ_{4358}, indicating anomalous dispersion. This hexanol and the hexenol from which it was prepared both yielded hydrogen phthalates of low dextrorotation. The *p*-xenylurethane of the hexenol obtained by hydrolysis of the *dl*-chloride can be separated into two fractions, one of which is the *p*-xenylurethane of γ-methyl-α-

ethylallyl alcohol (m. p. 102°) whilst the *other* (m. p. 82°) is presumably that of α-methyl-γ-ethylallyl alcohol. The hydrogen phthalate prepared from this hexenol does not crystallise, indicating that it is a mixture. The hexanol obtained from this hexenol yields a hydrogen phthalate and a *p*-xenylurethane, both of which can be separated into derivatives of ethyl-*n*-propyl- and methyl-*n*-butyl-carbinols. It being thus established that on hydrolysis of γ-methyl-α-ethylallyl chloride the corresponding alcohol and the anionotropic isomeride are formed, we have applied to the product the method of analysis described above. It is found that, starting with (+)-γ-methyl-α-ethylallyl alcohol, the product of hydrolysis of its chloride consists of 7·4% of (+)-γ-methyl-α-ethylallyl alcohol, 0·6% of (−)-α-methyl-γ-ethylallyl alcohol, and 92% of *dl*-material, which probably contains both isomerides in comparable amounts, since derivatives of both were isolated in substantial yield from the hydrolytic product of *dl*-hexenyl chloride.

The most significant feature of this result is the high proportion of racemisation, indicating that the chloride anion separates from the molecule before the hydroxyl ion becomes attached. The contrast of this behaviour with the high retention of optical activity in the intramolecular mutarotation rearrangement is marked. With regard to the optically active components of the product, the γ-methyl-α-ethylallyl alcohol has the same configuration as the original alcohol, because it is derived from it by two successive reactions of the type which cause inversion of configuration (accompanied by racemisation). The proportion of (−)-α-methyl-γ-ethylallyl alcohol formed is so small as to be of doubtful significance; it may be observed, however, that the small degree of optical activity retained on the C_γ atom is not likely to be due to shielding of this atom by the chlorine atom, since this, by analogy with the mutarotation reaction, would produce the (+)-alcohol.

Experimental.

dl-γ-Methyl-α-ethylallyl alcohol, prepared in 50% yield by the interaction of crotonaldehyde (0·9 mol.) and ethylmagnesium chloride, and dried over potassium carbonate, was distilled first in a vacuum and then at atmospheric pressure (Found: C, 72·9; H, 12·3. Calc.: C, 72·0; H, 12·1%). If the first distillation was omitted, the crude alcohol decomposed during the other distillation, water being eliminated. B. p. 44—45°/13 mm., 135—135·5°/760 mm.; $n_D^{23°}$ 1·4325, $d_4^{23°}$ 0·8346. Reif (*Ber.*, 1906, **39**, 1603; 1908, **41**, 2739) gives b. p. 133—134°/760 mm., $d_4^{25°}$ 0·8409, $n_D^{25°}$ 1·4312.

dl-*γ-Methyl-α-ethylallyl Hydrogen Phthalate.*—The *dl*-alcohol, phthalic anhydride, and pyridine in molecular proportions, were heated on a steam-bath for 1 hour. The cold homogeneous reaction mixture, when stirred with dilute hydrochloric acid and ice, yielded an oil which soon solidified (yield 80%). After being washed and dried, this product was sufficiently pure for resolution. It separates from carbon disulphide–light petroleum in small plates, m. p. 52—53° (Found, by titration: *M*, 245. $C_{14}H_{16}O_4$ requires *M*, 248). The *phthalate* remains unchanged when kept at room temperature for several months, or at 100° for 1½ hours, or when warmed at 80° for 2 hours in the presence of a trace (2½%) of phthalic acid. It slowly decomposes at room temperature in solution (*e.g.*, in benzene or carbon disulphide), depositing small quantities of phthalic acid after several months.

(+)-*γ-Methyl-α-ethylallyl Hydrogen Phthalate.*—Brucine (235 g.) was dissolved in a hot solution of the foregoing *dl*-ester (150 g.) in acetone (400 c.c.). The crystalline salt which separated was obtained optically pure after nine recrystallisations, each effected by adding acetone to the hot, concentrated solution of the salt in chloroform. Decomposition of the brucine salt occurs during recrystallisation if the materials are not thoroughly dried. *l*-Brucine (+)-γ-methyl-α-ethylallyl phthalate has m. p. 168°. (+)-γ-Methyl-α-ethylallyl hydrogen phthalate, obtained by decomposition of the brucine salt with hydrochloric acid, and crystallised from ether–light petroleum, has m. p. 70·5°; $[\alpha]_{5461}$ + 15·0° (*l*, 2; *c*, 5·0 in chloroform). A specimen of brucine salt which had been recrystallised only three times was decomposed and the resulting dextro-phthalate crystallised four times from ether light–petroleum; by this procedure also optically pure (+)-γ-methyl-α-ethylallyl hydrogen phthalate was obtained.

(−)-*γ-Methyl-α-ethylallyl Hydrogen Phthalate.*—After concentration, the first three mother-liquors from the brucine salt described above yielded a crop of crystals; these after three crystallisations from acetone had m. p. 125—126°, and when decomposed with hydrochloric acid yielded a hydrogen phthalate of m. p. 68—69°, $[\alpha]_{5461}$ − 14·7°. By three crystallisations of this ester from ether–light petroleum, optically pure (−)-γ-methyl-α-ethylallyl hydrogen phthalate, m. p. 70·5°, $[\alpha]_{5461}$ − 15·0° (*l*, 2; *c*, 5·0 in chloroform), was obtained.

(+)- *and* (−)-*γ-Methyl-α-ethylallyl Alcohols.*—The (+)- and the (−)-hydrogen phthalate were separately hydrolysed with sodium hydroxide (2·5 mols. of 5N) and heated in a current of steam. The alcohols were extracted with ether, dried with potassium carbonate, and distilled in a vacuum. The (+)-alcohol had $[\alpha]_{5893}$ + 12·38°, $[\alpha]_{5461}$ + 14·24°, $[\alpha]_{4358}$ + 28·65° (*l*, 2; *c*, 5·0 in carbon disulphide).

Reduction of γ-Methyl-α-ethylallyl Alcohol.—The alcohol was reduced with hydrogen at 2 atm. in dry ether with a platinum catalyst (Short, *J. Soc. Chem. Ind.*, 1936, **55**, 14T). (i) *dl*-Alcohol, freshly prepared from the hydrogen phthalate, yielded ethyl-*n*-propylcarbinol, b. p. 132·5—133·5°, $d_4^{20°}$ 0·8193. (ii) *dl*-Alcohol,

prepared from the hydrogen phthalate and kept for 2 years, yielded a hexanol, b. p. 131—133°, $d_4^{20°}$ 0·8181; Pickard and Kenyon (J., 1913, **103**, 1923) give $d_4^{20°}$ 0·8213; Ginnings and Webb (*J. Amer. Chem. Soc.*, 1938, **60**, 1389) give b. p. 134·5—135°/760 mm., $d_4^{25°}$ 0·8143. (iii) (+)-Alcohol, having $[\alpha]_{5461}^{21°}$ + 14·91° (96% optically pure), yielded (+)-ethyl-*n*-propylcarbinol, b. p. 131—133°. $[\alpha]_{5893}^{20°}$ + 6·81°, $[\alpha]_{5461}^{20°}$ + 7·79°, $[\alpha]_{4358}^{20°}$ + 12·41° (*l*, 0·25).

Ethyl-n-*propylcarbinyl Hydrogen Phthalate.*—(i) The *dl*-carbinol described in (i) above was heated with phthalic anhydride (1 mol.) at 110—120° for 7 hours; the ester thereby obtained was crystallised from ether–light petroleum, m. p. 75—76°. Pickard and Kenyon (*loc. cit.*) give m. p. 76—77°. (ii) The ester similarly prepared from the (+)-carbinol described in (iii) above had m. p. 48—49°, $\alpha_{5893}^{20°}$ + 9·31°; $\alpha_{5780}^{20°}$ + 10·19°; $\alpha_{5461}^{20°}$ + 11·26°; $\alpha_{4358}^{20°}$ + 18·26° (*l*, 2; *c*, 5·0 in chloroform).

Methyl-n-*butylcarbinyl Hydrogen Phthalate.*—The *dl*-carbinol, b. p. 137—140°, $d_4^{20°}$ 0·8150 (Pickard and Kenyon, J., 1911, **99**, 45, give b. p. 136°, $d_4^{20°}$ 0·8150), was prepared by the interaction of acetaldehyde and *n*-butylmagnesium bromide. The hydrogen phthalate, prepared in the usual manner, crystallised in needles, m. p. 48°, from ether–light petroleum.

dl-*γ-Methyl-α-ethylallyl acetate*, prepared by Einhorn's method, had b. p. 54—56°/17 mm., 152—154°/760 mm., $n_D^{19°}$ 1·4230, $d_4^{15°}$ 0·8931 (Found: C, 66·9; H, 9·8. $C_8H_{14}O_2$ requires C, 67·5; H, 9·9%), and the *benzoate*, prepared similarly, had b. p. 144—145°/20 mm., $n_D^{19°}$ 1·5076; $d_4^{19°}$ 1·0055 (Found: C, 76·4; H, 7·8. $C_{12}H_{16}O_2$ requires C, 76·45; H, 8·0%).

dl-*γ-Methyl-α-ethylallyl chloride* was prepared by the slow addition of thionyl chloride (1·1 mols.) to a mixture of the *dl*-alcohol with quinoline (1 mol.) in ether at 0°, the solution being filtered while cold. It has b. p. 30°/13 mm., 100°/370 mm., and 123—124°/760 mm. (slight decomp.); $n_D^{20°}$ 1·4400 (Found: C, 61·0; H, 9·6; Cl, 28·2. $C_6H_{11}Cl$ requires C, 60·7; H, 9·4; Cl, 29·9%). The corresponding (−)-chloride, prepared from the (+)-alcohol having $[\alpha]_{5461}^{20·5°}$ + 15·8°, had $\alpha_{5893}^{19°}$ − 11·25°, $\alpha_{5780}^{19°}$ −12·65°, $\alpha_{5461}^{19°}$ − 14·75°, $\alpha_{4358}^{19°}$ − 28·3° (*l*, 0·5).

Hydrolysis of dl-*γ-Methyl-α-ethylallyl Chloride.*—Over a period of 3 days calcium carbonate (5 g.) was added to a mixture of the chloride (6 g.) and water (15 g.) with occasional shaking. The resulting hexenol was dried with potassium carbonate and distilled in a vacuum; 20% had b. p. up to 47°, 60% b. p. 47—49°, 20% b. p. 49—50°/12 mm. All the fractions had $n_D^{19·5°}$ 1·4345. Total yield, 4 g.

The *p*-xenylurethane of *dl-γ*-methyl-α-ethylallyl alcohol was prepared by heating the freshly prepared *dl*-alcohol (0·5 g.) with *p*-xenylcarbimide (1 g.) at 100° for 1 hour and extraction with ether. It separated from ether–light petroleum in long colourless needles, m. p. 102°. When prepared from *dl*-carbinol that had stood for 2 years, it afforded on fractional crystallisation two crops of crystals; the major crop had m. p. 102—103°, and a small quantity (25%) was obtained with an apparently constant m. p. 84—86°.

p-*Xenylurethane of the Product of Hydrolysis of* dl-*γ-Methyl-α-ethylallyl Chloride.*—The hexenol (5 g.) and *p*-xenylcarbimide (10 g.) were treated as before, and after extraction with ether the product was fractionally crystallised from ether–light petroleum. The higher-melting crop had m. p. 102—103°, and mixed m. p. with the p-*xenylurethane* (see above) of authentic *dl-γ*-methyl-α-ethylallyl alcohol, 102° (Found: C, 78·9; H, 7·4. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·2%). The other final crop had m. p. 81—82° (Found: C, 77·9; H, 7·4%).

The p-*xenylurethanes* of *dl*-ethyl-*n*-propylcarbinol and *dl*-methyl-*n*-butylcarbinol separated from ether–light petroleum in colourless needles, m. p. 135° (Found: N, 4·7. $C_{19}H_{23}O_2N$ requires N, 4·7%), and m. p. 91—92° (Found: N, 4·7%), respectively.

p-*Xenylurethane of the Reduced Product of Hydrolysis of* dl-*γ-Methyl-α-ethylallyl Chloride.*—The hexenol (4 g.) was reduced with hydrogen, distilled, converted into the *p*-xenylurethane, and fractionally crystallised from ether–light petroleum. One crop had m. p. 132—133°, and, when mixed with the *p*-xenylurethane of *dl*-ethyl-*n*-propylcarbinol, m. p. 131—132°; the other had m. p. 91—92° and, when mixed with the *p*-xenylurethane of *dl*-methyl-*n*-butylcarbinol, m. p. 90—91°.

Hydrogen Phthalate of the Reduced Product of Hydrolysis of dl-*γ-Methyl-α-ethylallyl Chloride.*—The reduced product (3·8 g.), heated with phthalic anhydride (5·7 g.) at 110—120° for 7 hours, gave the hydrogen phthalate which was purified *via* its sodium salt and fractionally crystallised from ether–light petroleum. One crop had m. p. 73° and, when mixed with dl-*ethyl*-n-*propylcarbinyl hydrogen phthalate*, m. p. 73—74·5° (*M*, by titration, 251. $C_{14}H_{18}O_4$ requires *M*, 250). The other crop had m. p. 46—48° and, when mixed with dl-*methyl*-n-*butylcarbinyl hydrogen phthalate*, m. p. 45—47° (Found: *M*, 252).

Hydrolysis of (−)-*γ-Methyl-α-ethylallyl Chloride.*—The (−)-chloride (5·5 g.), having $\alpha_{5461}^{18·5°}$ − 6·55° (*l*, 0·5) [prepared from the (+)-alcohol (10 g.) having $[\alpha]_{5461}^{21°}$ + 6·56°], was hydrolysed as before, giving a hexenol having $\alpha_{5893}^{18°}$ − 0·11°, $\alpha_{5780}^{18°}$ − 0·10°, $\alpha_{5461}^{18°}$ − 0·07°, $\alpha_{4358}^{18°}$ − 0·03°, (*l*, 0·5). This was reduced to the hexanol (1·5 g.) having b. p. 132—137°, $\alpha_{5893}^{20°}$ + 0·04°, $\alpha_{5461}^{20°}$ + 0·02°, $\alpha_{4358}^{20°}$ ± 0·00° (*l*, 0·25). This gave a hydrogen phthalate having (without recrystallisation) $[\alpha]_{5893}$ + 0·20°, $[\alpha]_{5461}$ + 0·07° in chloroform (*l*, 2; *c*, 7·5). The ethereal washings from the alkaline solution of this hydrogen phthalate were optically inactive.

The quotient for λ 5893, 0·20/0·16 = 1·25, corresponds with the ratio 93% of *d*-ethyl-*n*-propylcarbinol to 7% of *l*-methyl-*n*-butylcarbinol, and such a mixture of optically pure components would have $\alpha_{5893}^{20°}$ + 4·7° (*l*, 1·0) (see figure). The initial (+)-carbinol was 42% optically pure, so that for optically pure starting material the rotation of the final hexanol would be $\alpha_{5893}^{20°}$ + 0·38° (*l*, 1·0) or 8% of the theoretical. Hence, on

tautomerisation of (+)-α-ethyl-γ-methylallyl alcohol by conversion into the chloride and subsequent hydrolysis, there was 92% racemisation, 7·4% unchanged, and 0·6% converted into (−)-α-methyl-γ-ethylallyl alcohol.

Methyl γ-Methyl-α-ethylallyl Ether.—(i) *From γ-methyl-α-ethylallyl alcohol.* To the alcohol (5 g., $\alpha^{22°}_{5461}$ − 2·5°; *l*, 0·5) in dry ether (30 c.c.), potassium (1·6 g.) was added; after standing overnight, the unreacted potassium was removed, and methyl iodide (7 g.) added to the solution. When the rapid reaction was complete, the solution was washed with water, dried, the ether evaporated, and the residue distilled at normal pressure. To remove unchanged alcohol, the distillate (2·6 g.) was warmed with phthalic anhydride (3 g.) and pyridine (2 g.), and the hydrogen phthalic ester removed by extraction with sodium carbonate. The residual *methyl γ-methyl-α-ethylallyl ether* was distilled at normal pressure, b. p. 110—115°, yield 1·5 g., $n^{20°}_{D}$ 1·4110, $\alpha^{23°}_{5461}$ + 6·88° (*l*, 0·5) (Found: C, 72·5; H, 12·3. $C_7H_{14}O$ requires C, 73·7; H, 12·3%).

(ii) *From (−)-γ-methyl-α-ethylallyl hydrogen phthalate.* The phthalate {8 g., $[\alpha]_{5461}$ − 6·0° in chloroform; the same specimen from which the alcohol used in (i) was obtained by hydrolysis} was heated under reflux with anhydrous methyl alcohol (50 g.) for 32 hours, and the reaction mixture distilled at ordinary pressure. The distillate, diluted with twice its volume of dry ether, was mixed with powdered calcium chloride (60 g.) and left overnight. After filtration, and removal of the ether by evaporation, the residual methyl hexenyl ether was distilled; b. p. 110—112°, $n^{22°}_{D}$ 1·4180, $\alpha^{21°}_{5461}$ − 0·18° (*l*, 0·5); yield 1·0 g.

dl-*γ-Methyl-α-ethylallyl* p-*nitrobenzoate*, prepared from the alcohol (5 g.) by Einhorn's method, separates from light petroleum in pale yellow flakes (5 g.), m. p. 35—37° (Found: N, 5·4. $C_{13}H_{15}O_4N$ requires N, 5·6%).

Surface tensions were determined by the method of maximum bubble pressure (Sugden, *op. cit.*), the apparatus being calibrated by means of benzene.

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BATTERSEA POLYTECHNIC, LONDON, S.W. 11. [*Received, October 22nd*, 1941.]

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6. *A Method for the Accurate Analysis of Gaseous Mixtures.*

By C. H. BAMFORD and R. R. BALDWIN.

A method of gas analysis is described which is free from the main sources of error inherent in standard methods, and gives results reliable to 0·03% or better. The method depends on pressure measurements after separation of constituents by cooling or chemical oxidation changes, no confining liquid or absorbents being used. The apparatus has considerable flexibility, being suitable for the precise analysis of many kinds of gaseous mixtures.

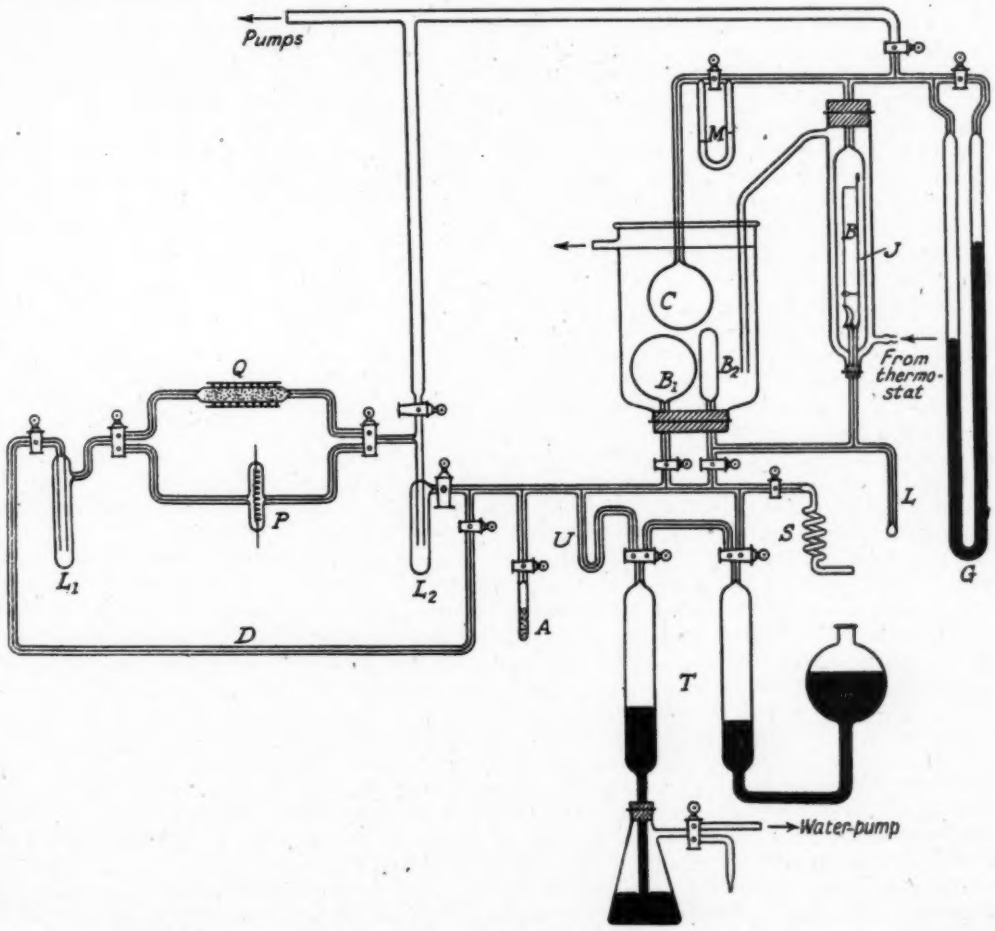
SEVERAL inherent sources of error render ordinary methods of gas analysis unsuitable for adaptation to precision measurements on mixtures containing a number of constituents. The use of liquid absorbents is necessarily accompanied by uncertainty, it is practically impossible to apply complete corrections for the physical solubility of the various gases in the reagents, and components estimated towards the end of the analysis may be in considerable error through losses incurred during repeated contacts with liquids. These difficulties cannot be entirely overcome by the use of solid absorbents. Further troubles are encountered when moist mercury menisci have to be used, on account of the difficulty of keeping the volume of liquid and also the shape of the meniscus the same. In addition, the principle of measurement by contraction is in itself unsatisfactory, especially if only small percentages of the gas are present. All these difficulties are, of course, enhanced if only a small quantity of the initial gas is available.

The authors' experience has been that analyses reproducible to 0·1—0·2% for the main constituents of the mixture can be obtained with a standard Bone and Wheeler apparatus, but the absolute accuracy is generally much less than this. The presence or absence of constituents in concentrations of 0·1—0·2% is always in some doubt. The present apparatus was designed particularly for the analysis of mixtures containing about 80% of inert gas, the errors for the individual constituents being less than 0·03%. The method may, however, be applied equally successfully to other mixtures.

EXPERIMENTAL.

Apparatus and Method.—The method of analysis consists in the successive quantitative conversion of the components into carbon dioxide and/or water, which are measured separately. Dependence on contraction measurements is thus avoided, although the latter may be used as checks if desired. The measurement of carbon dioxide and water is effected by determining the pressure they exert in one of two standard volumes, which in the present apparatus have a ratio of about 7 : 1. This enables either large or small amounts of gas to be measured accurately.

The apparatus is shown in the diagram. The two measuring bulbs B_1 and B_2 are immersed in a thermostat and may be put into communication with a thermostated Bourdon gauge B of the Foord type (*J. Sci. Instr.*, 1934, **11**, 126) or a Toepler pump T. The Bourdon gauge can be read to within 0·05 mm. of mercury. The volumes of the bulbs used depend on the amount of gas available. In the present apparatus they are about 80 c.c. and 10 c.c. respectively, but there is no reason why they should not be considerably reduced. The Toepler pump serves to evacuate the gas from the bulbs and enables it to be passed either round the circuit DL_1PL_2, comprising two liquid-air traps and a tube containing a platinum spiral P, or round the alternative circuit DL_1QL_2 which includes a quartz tube Q containing copper oxide. Both the platinum spiral and the quartz tube may be heated electrically. To reduce the dead space, capillary tubing of 1 mm. internal diameter is used wherever possible. The jacket J of the Bourdon gauge is connected to a wide mercury manometer G, which serves to measure the initial pressure of the gas. The accurate adjustment of the pressure



in the jacket, which is necessary for contraction measurements, is accomplished by using a constant-pressure bulb C, which may be put into communication with the jacket through a small manometer M, containing low-vapour-pressure oil. The pressure in the jacket may in this manner be reproduced to within 0·02 mm. of mercury. The bulb C is immersed in the same thermostat as B_1 and B_2: this eliminates errors due to temperature fluctuations in the thermostat, which would otherwise have to be controlled to within 0·01° to obtain a reliable measurement of the contraction. The whole apparatus may be evacuated by a three-stage mercury diffusion pump backed by a Hyvac pump.

The two standard volumes comprise (1) the bulbs B_1 and B_2 and the spoon of the Bourdon gauge, called the " large " volume in the sequel, and (2) B_2 and the spoon, called the " small " volume.

To illustrate the method of analysis the procedure with a typical gas specimen is described.

(a) *Measurement of Initial Pressure.*—The gas is admitted to the evacuated system through the spiral S cooled in a solid carbon dioxide–ether mixture, to remove water vapour and other substances of low volatility. Any condensate obtained may be examined as described under (f) below. The initial gas is admitted to the

large volume so as to give a suitable reading of the Bourdon gauge when the standard pressure is applied to the jacket. This pressure may be 300—500 mm., and it is measured to one part in 2000 parts by the mercury gauge. The sum of the Bourdon reading and the standard pressure gives the initial pressure. After measurement, the gas is transferred to the Toepler pump.

(b) *Carbon Dioxide and Hydrocarbons other than Methane.*—(i) *Carbon dioxide if present alone.* The traps L_1 and L_2 are cooled in liquid air, and the gas in T is passed slowly round the circuit DL_1PL_2 for about 10 minutes, thus condensing out the carbon dioxide. The permanent gas is evacuated into the Toepler, and the condensate in the traps distilled to the small limb L by cooling the latter in liquid air. The bulbs are then isolated from the rest of the apparatus, and L warmed to $-78°$. The carbon dioxide vaporised is measured in the suitable standard volume by means of the Bourdon gauge*. The gas is then rejected. If it is desired to measure the contraction accompanying the removal of the carbon dioxide, the residual gas in T is transferred to the large volume and measured with the Bourdon gauge, the standard pressure being used.

(ii) *Carbon dioxide present with hydrocarbons.* The condensate in this case will contain, in addition to carbon dioxide, hydrocarbons, and these, being volatile at $-78°$, will be measured with the dioxide. If ethylene is present, there is also the possibility that the whole of this compound will not remain condensed during evacuation with the Toepler pump, since its vapour pressure at $-196°$ is about 0·003 mm. To ensure that no appreciable quantity of olefin remains in the permanent gas, the latter is passed a few times through the capillary tube U immersed in liquid nitrogen, by means of the Toepler pump. By one or two operations of the latter, U can then be evacuated. After this treatment the pressure of ethylene in the residue cannot be greater than about 0·006 mm., which is not appreciable. The condensates in the traps and capillary are united, distilled into L, and measured. The hydrocarbon in the mixture is then oxidised by distilling the latter backwards and forwards through the copper oxide furnace at about 700° for about 10 minutes, the traps L_1 and L_2 being used for this purpose. The whole is then recondensed in L, and the carbon dioxide vaporised by warming to $-78°$. It is then measured and abandoned. The water formed during oxidation is next estimated by allowing the limb to warm to room temperature, care being taken that the whole of the liquid is vaporised. Tests have shown that a complete separation of carbon dioxide and water is obtained in this way, and that the presence of water does not interfere at all with the measurement of the carbon dioxide. If the nature of the hydrocarbon present is known, the figures obtained permit it to be estimated. If unknown hydrocarbons are present, and identification is necessary, the analysis cannot be carried out so accurately. The best procedure would appear to be the condensation of the mixture of carbon dioxide and hydrocarbon in the soda-lime tube A, after which the hydrocarbon is taken back to L and measured. It is then identified by combustion over copper oxide as described above. To check the results so obtained it is desirable to repeat the estimation, combusting the whole of the condensate without previous separation of carbon dioxide.

(c) *Oxygen.* This may be accurately determined by combustion with carbon monoxide and/or hydrogen over the platinum spiral. If the gas contains carbon monoxide and hydrogen in excess of the oxygen, the combustion is carried out by circulating the residual gas from (b) over the spiral maintained at a very dull red heat, the traps being cooled in liquid air. The carbon dioxide and water formed are measured as described in (b) (ii), and determination of the contraction [as in (a)] is used as a check. The oxygen content is given by $\frac{1}{2}(CO_2 + H_2O)$ and $\frac{1}{3}$ (contraction). If there is an excess of oxygen initially, a known pressure of carbon monoxide may be added.

(d) *Carbon monoxide and hydrogen.* These gases are quantitatively oxidised by copper oxide at 300°. The residual gas from (c) is circulated over the oxide for about 20 mins., with L_1 and L_2 in liquid air. After evacuation of the remaining gas, the products are measured as usual, together with the contraction if desired.

(e) *Methane.* The oxidation of methane to carbon dioxide and water by copper oxide at about 900° was found to be quite satisfactory. Circulation of the gas through the furnace for about 20 mins. ensures complete oxidation. The products and contraction are measured in the usual way.

(f) *Examination of the condensate in the spiral at* $-78°$. The exact treatment of the condensate must, of course, depend on the constituents present. The carbon content may be determined by distilling the substance through the copper oxide furnace at 700° a few times and measuring the carbon dioxide formed. If the condensate is a single compound, *e.g.*, water, it may be distilled to L at once and measured.

The methods described above have been thoroughly tested on various mixtures of known composition. Some figures are given below, together with those for a typical duplicate analysis of a gas specimen, in order to illustrate the order of accuracy obtainable.

	Percentages by volume.			
	Synthetic mixture.		Gas sample, duplicate analyses.	
Constituent.	Used.	Found.		
CO_2	6·58	6·61	9·23	9·21
C_5H_{12} ...	—	—	0·04	0·04
O_2	0·25	0·24	0·20	0·21
CO	4·20	4·23	8·05	8·04

	Percentages by volume.			
	Synthetic mixture.		Gas sample, duplicate analyses.	
Constituent.	Used.	Found.		
H_2	2·72	2·70	3·59	3·61
CH_4	0·51	0·51	0·07	0·06
N_2	85·74	85·71	78·83	78·83

* If the small volume is used, a correction should be applied for the change in the ratio of the apparent volumes of the bulbs due to the cooling of L to $-78°$.

The method may readily be extended to the analysis of mixtures of gases other than those mentioned above, the details depending on the nature of the problem. The following additional examples of the use of the apparatus may be mentioned. Small percentages of carbonaceous gas in an inert atmosphere may be easily estimated to 0·005%; *e.g.*, the carbon dioxide content of samples of atmospheric air has been determined as 0·03%, in agreement with the accepted figure. Various methods for the estimation of oxygen have been developed, giving the oxygen content of the air as 20·94 ± 0·04%.

In order to shorten the time required for an analysis, it would be advantageous to use one limb of the Toepler pump as the thermostated large volume, as this would dispense with the rather slow process of evacuating the bulbs with this pump. However, the apparatus has been described as originally used, in the hope that it may provide a basis for the solution of problems of gas analysis confronting other workers.

[LABORATORY OF PHYSICAL CHEMISTRY, CAMBRIDGE. [*Received, November 4th*, 1941.]

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7. *The Cyclic Methyleneimines. Part IV. Hydrolysis of Quaternary Compounds. Preparation of Secondary Amines.*

By JOHN GRAYMORE.

Two products have been obtained by the action of a dry ethereal solution of benzenesulphonyl chloride on *NN'N''*-trimethyltrimethylenetriamine, also in dry ether. One has been identified as *methylaminobismethylenebenzenesulphonmethylamide*. The other, an unstable substance, has been shown to be a halogen derivative of a formaldehyde-methylamine condensation product.

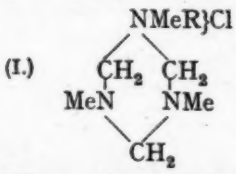
p-Toluenesulphonyl chloride under similar conditions has also given the latter product. *Methylenebis*-p-*toluenesulphonmethylamide* and *p*-toluenesulphonmethylamide have also been obtained in this reaction.

FURTHER evidence is now recounted in support of the suggestion (Part III; J., 1941, 39) that addition of alkyl halides to the cyclic methyleneimines is followed by opening of the methyleneimino-ring.

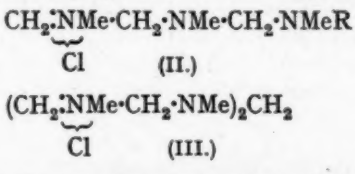
When benzenesulphonyl chloride was added to *NN'N''*-trimethyltrimethylenetriamine in dry ethereal solution, a crystalline product separated. On hydrolysis in acid solution, this substance gave methylamine and formaldehyde as sole products. The crystals were extremely unstable in moist air and could not be dried in a vacuum without decomposition, so accurate analytical results were difficult to obtain.

When allowed to evaporate in the open or in contact with water, the ethereal solution remaining gave an excellent yield of *bis(benzenesulphonmethylamidomethyl)methylamine* (IV; R = Ph·SO_2). Although there is, as yet, no direct experimental evidence, it seems probable that the base first adds benzenesulphonyl chloride (I; R = Ph·SO_2). In this connection it may be noted that addition compounds of hexamethylenetetramine with acid chlorides, *e.g.*, $(CH_2)_6N_4,C_6H_5{\cdot}COCl$, have been reported (Hartung, *J. pr. Chem.*, 1892, **46**, 1). Addition of a further molecule of benzenesulphonyl chloride would give a diquaternary ammonium compound, which by loss of methylene dichloride could pass into bis(benzenesulphonmethylamidomethyl)methylamine (IV). However, this would not explain the formation of the second product, since methylene dichloride has no action on trimethyltrimethylenetriamine.

It is suggested that the addition of benzenesulphonyl chloride is followed by opening of the ring, giving (II; R = Ph·SO_2). Interaction of the latter with trimethyltrimethylenetriamine or methylenemethylamine would result in the formation of bis(benzenesulphonmethylamidomethyl)methylamine (IV) and *methylenebisdimethyldimethylenediamine chloride* (III). The analytical data suggested the separation of the latter in a form containing 4 mols. of formaldehyde. This is not improbable, since trimethyltrimethylenetriamine, as usually prepared, contains appreciable quantities of formaldehyde.

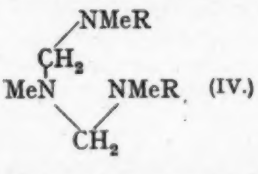


(I.)



(II.)

(III.)



(IV.)

p-Toluenesulphonyl chloride, added to trimethyltrimethylenetriamine in dry ether, gave an unstable crystalline compound, the properties of which are identical with those of the compound obtained with benzenesulphonyl chloride. Evaporation of the ethereal solution, however, gave a syrup from which

p-toluenesulphonmethylamide and *methylenebis*-p-*toluenesulphonmethylamide*, $CH_2(NMe{\cdot}SO_2{\cdot}C_7H_7)_2$, were separated. These probably result from the breakdown of a compound of type (IV). Bis(benzenesulphonmethylamidomethyl)methylamine readily decomposed in acid or alkaline solution to give formaldehyde, methylamine, and benzenesulphonmethylamide.

Attempts to prepare sulphonilamides of type (IV) have so far met with little success.

Experimental.

Action of Benzenesulphonyl Chloride on NN'N''-*Trimethyltrimethylenetriamine*.—Benzenesulphonyl chloride (5 c.c.) in dry ether was mixed with a dry ethereal solution of the base (5 c.c.) and kept for 2 days. The white crystalline *product* (III), m. p. 118—120° (decomp.), was removed and washed quickly with dry ether (Found: C, 42·4; H, 8·0; N, 14·9, 15·5; Cl, 17·7, 18·4. $C_9H_{22}N_4Cl_2,4CH_2O$ requires C, 41·4; H, 8·0; N, 14·9; Cl, 18·8%). It was readily soluble in chloroform, and could be reprecipitated by ether. It decomposed readily in moist air, giving formaldehyde. When dried in a vacuum at the ordinary temperature, it lost weight and an odour resembling that of methyl *iso*cyanide developed. When its solution in hydrochloric acid was steam-distilled to remove formaldehyde, evaporated to dryness, and extracted with chloroform, it yielded methylamine hydrochloride, m. p. and mixed m. p. 225°. On distillation of its aqueous solution formaldehyde was copiously evolved. The aqueous distillate, evaporated with hydrochloric acid, gave formaldhyde and methylamine hydrochloride; the latter was identified by means of its derivative with 2 : 4-dinitrochlorobenzene.

The ethereal solution, left to evaporate spontaneously, slowly deposited needle-like crystals. After being washed with water and small quantities of ether, *bis*(*benzenesulphonmethylamidomethyl*)*methylamine* was recrystallised from chloroform–ether, forming needles, m. p. 122—123°, insoluble in water and slightly soluble in ether (Found: C, 51·6; H, 5·8; S, 16·0. $C_{17}H_{22}O_4N_3S_2$ requires C, 51·4; H, 5·8; S, 16·1%). The substance dissolved readily in cold hydrochloric acid, but decomposed, giving formaldehyde, in boiling acid solution. Distilled from sodium hydroxide, it decomposed slowly, giving a distillate in which formaldehyde and methylamine were easily detected. When acidified, the residual liquor gave benzenesulphonmethylamide as an oil which slowly solidified, m. p. 29—30° (Found: N, 8·0. Calc. for $C_7H_9O_2NS$: N, 8·2%).

p-*Toluenesulphonyl Chloride and the Base*.—Trimethyltrimethylenetriamine (5 g.) in dry ether was mixed with a solution of *p*-toluenesulphonyl chloride (6 g.) in dry ether. The solution developed an immediate turbidity and after several days deposited a crystalline substance, m. p. 118—122°, which exhibited the properties of the product (III) above (Found: N, 15·2. Calc. for $C_9H_{22}N_4Cl_2,4CH_2O$: N, 14·9%).

The syrupy liquid left on spontaneous evaporation of the residual ethereal solution in air was treated with cold dilute hydrochloric acid to remove any residual base. The crystalline solid remaining was collected, extracted with cold sodium hydroxide solution, and then warmed gently with sodium hydroxide solution until the smell of *p*-toluenesulphonyl chloride was not apparent. The residual *methylenebis*-p-*toluenesulphonmethylamide* crystallised from ether in cubes (0·7 g.), m. p. 117—118° (Found: C, 53·6; H, 5·5; S, 17·1. $C_{17}H_{22}O_4N_2S_2$ requires C, 53·4; H, 5·75; S, 16·8%). When boiled with dilute acid, it decomposed, giving formaldehyde and *p*-toluenesulphonmethylamide (m. p. and mixed m. p.). The sodium hydroxide extracts, on acidification, gave *p*-toluenesulphonmethylamide (m. p. and mixed m. p.).

Thanks are expressed to the Chemical Society for a grant. The author is indebted to Dr. G. Weiler for most of the analyses.

Stockport College for Further Education. [*Received, July 21st,* 1941.]

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8. *The Decomposition of Arylazo-β-naphthylamines by Sodium Nitrite and Glacial Acetic Acid.*

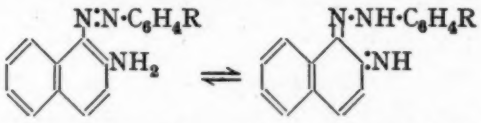
By Herbert H. Hodgson and Clifford K. Foster.

Twenty-nine arylazo-β-naphthylamines have been decomposed by sodium nitrite in the presence of hot glacial acetic acid. The products are usually mixtures of the arylazo-β-naphthyl acetate and the arylazo-β-naphthol, but some of the amines having electron-attracting substituents in the *o*-position of the aryl residue give the arylazo-β-naphthol only. The mechanism of the general reaction is discussed.

Although the substances formed when diazonium compounds react with β-naphthylamine behave like diazoamino-derivatives towards hydrochloric acid (Lawson, *Ber.*, 1885, **18**, 796), it has long been established that they are aminoazo-compounds; the presence of the amino-group, however, has always been difficult to prove. Meldola (J., 1884, **45**, 117), after a study of the action of nitrous acid on

m-nitrobenzeneazo-β-naphthylamine, concluded that a nitroso-derivative was formed and that the amino-group was not present, but Meldola and East (J., 1886, **49**, 463) reported that the nitroso-compounds were in fact acetates, and that the action of sodium nitrite in the presence of acetic acid (glacial) on the foregoing β-naphthylamine derivative and on *p*-nitrobenzeneazo-β-naphthylamine was to displace the amino-group by the acetoxy-group, possibly by the intermediate formation of an unstable diazonium compound.

Zincke and Lawson (*Ber.*, 1887, **20**, 2896), however, describe the actual diazotisation of benzeneazo-β-naphthylamine and some reactions of the diazonium salts, so under the conditions employed the amino-group must have been present; no mention, however, is made of coupling, *e.g.*, with alkaline β-naphthol. In view of the difficulties encountered in diazotising azo-β-naphthylamine compounds,



the current view that there is tautomerism between the aminoazo- and the iminohydrazone structure, with a preponderance of the latter form, is doubtless correct; under special conditions the amino-group can be detected, and its diazotisation performed.

In continuation of this study, Meldola's work has been confirmed for *m*- and *p*-nitrobenzeneazo-β-naphthylamines and extended to 27 other β-naphthylamine derivatives (Table I). Some of the amines, and in particular those with electron-attracting groups, readily yield the acetoxy-compounds

TABLE I.

Arylazo-β-naphthylamines.

The colour produced by concentrated sulphuric acid is given after the analysis, and for a known compound after the reference.

Diazotised amine.	Crystalline form and solvent.	M. p.	% N found.	% N required.	Reference.
m-Fluoroaniline	Orange leaves, dilute alcohol	85°	16·1	15·9	(Violet)
Aniline	Red needles, glacial acetic acid	103	—	—	Lawson, *Ber.*, 1885, **18**, 798, gives m. p. 102—104° (Red-violet)
p-Toluidine	Orange hexagonal prisms, methyl alcohol	114	—	—	Norman, J., 1912, **101**, 1919, gives m. p. 112° (Red-violet)
p-Chloroaniline	Scarlet prisms, glacial acetic acid	116	—	—	Meldola, Forster, J., 1891, **59**, 690, give m. p. 116° (Blue-violet)
p-Fluoroaniline	Orange-red plates, alcohol	120	16·1	15·9	(Red-violet)
o-Toluidine	Deep red parallelepipeds, alcohol	126	—	—	Fischer, *J. pr. Chem.*, 1921, **104**, 113, gives m. p. 125—126° (Red-violet)
p-Anisidine	Deep orange prisms, glacial acetic acid	132—133	—	—	Charrier, Ferreri, *Gazetta*, 1913, **43**, ii, 231, give m. p. 127° (Red-violet)
o-Anisidine	Deep red prisms, alcohol	134	—	—	Sachs, *Ber.*, 1885, **18**, 3130, gives m. p. 133° Meldola, Forster, J., 1891, **59**, 697, give m. p. 129° (Violet-red)
p-Bromoaniline	Bright red needles, alcohol	135	—	—	Meldola, Forster, J., 1891, **59**, 690, give m. p. 135° (Blue-violet)
o-Chloroaniline	Red needles, glacial acetic acid	142	—	—	Norman, J., 1919, **115**, 675, gives m. p. 151° (Blue-violet)
β-Naphthylamine	Brown needles, xylene	149	—	—	Lawson, *Ber.*, 1885, **18**, 2422, gives m. p. 149° (Blue)
α-Naphthylamine	Dark brown microscopic needles, alcohol	154	—	—	Elter, *Gazzetta*, 1915, **45**, ii, 315, gives m. p. 154° (Greenish-blue)
m-Chloroaniline	Red needles, glacial acetic acid	160	15·1	14·9	(Blue-violet)
2 : 5-Dichloroaniline	Red needles, glacial acetic acid	168	13·5	13·3	(Blue)
p-Iodoaniline	Small red-brown prisms, alcohol	170	11·5	11·3	(Blue)
p-Nitroaniline	Gold needles, alcohol	180	—	—	Meldola, J., 1883, **43**, 431, gives m. p. 180° (Violet-blue)
m-Nitroaniline	Orange needles, alcohol	182	—	—	Meldola, East, J., 1888, **53**, 463, give m. p. 182° (Violet)
Anthranilic acid	Carmine-red needles, benzene	183	—	—	Fischer, *J. pr. Chem.*, 1923, **107**, 32, gives m. p. 182—185° (Violet-blue)
4-Bromo-3-nitroaniline	Dark green masses, toluene	190	15·2	15·1	(Blue)
p-Aminophenol	Orange needles, dilute alcohol	192	—	—	Sachs, *Ber.*, 1885, **18**, 3129, gives m. p. 192—193° (Red-violet)
o-Nitroaniline	Bronze scales, glacial acetic acid	198	—	—	Meldola, Hughes, J., 1891, **59**, 375, give m. p. 198° (Blue-violet)
2-Nitro-*p*-toluidine	Brown needles, glacial acetic acid	199	18·5	18·3	(Blue-violet)
5-Nitro-1-naphthylamine	Dark brown microscopic needles, chlorobenzene	212	16·2	16·4	(Greenish-blue)
4-Nitro-1-naphthylamine	Black needles with greenish tinge, chlorobenzene	214	16·6	16·4	(Orange-red)
3-Nitro-*p*-toluidine	Dark bronze needles, glacial acetic acid	226	—	—	Norman, J., 1919, **115**, 678, gives m. p. 224° (Greenish-blue)
4-Chloro-2-nitroaniline	Dark bronze needles, toluene	255	17·2	17·2	(Blue-violet)
4-Bromo-2-nitroaniline	Dark bronze needles, toluene	259	15·4	15·1	(Greenish-blue)
p-Aminobenzoic acid	Minute, red, diamond-shaped crystals, benzene	264	—	—	Fischer, *J. pr. Chem.*, 1923, **107**, 34, gives m. p. 263—264° (Violet-blue)
Picramic acid	Dark green needles, nitrobenzene	274	20·1	19·9	(Blue-grey)

under Meldola's conditions, whereas those with electron-repelling groups yield tars. From these tars acetoxy-compounds could not be isolated, owing to experimental difficulties, though they were un-

doubtedly present, and on hydrolysis with alcoholic hydrochloric acid almost the entire product was obtained as arylazo-β-naphthol.

In all cases, the action of sodium nitrite and glacial acetic acid on arylazo-β-naphthylamines appears to be replacement of the amino- by the acetoxy-group, subsequent hydrolysis by the water formed in the reaction converting a portion of the acetate into the arylazo-β-naphthol. From 2 : 5-dichloro-, *o*-nitro-, and *o*-carboxy-benzeneazo-β-naphthylamines the whole product is the arylazo-β-naphthol, but this is readily accounted for by ease of hydrolysis; *e.g.*, 4-bromo-2-nitrobenzeneazo-β-naphthyl acetate, which is formed from 4-bromo-2-nitrobenzeneazo-β-naphthylamine, is hydrolysed at once when attempts are made to crystallise it from acetic acid containing water. Moreover, in those cases where the crystalline acetoxy-compounds separate directly from the reaction mixture, the solution always contains a mixture of acetoxy-compound and the arylazo-β-naphthol, which is completely hydrolysed to the latter compound. Diminished solubility of the acetoxy-compound appears to be favoured by the presence of electron-attracting groups.

The mechanism of the reaction under review therefore appears to be initial diazotisation of the amino-group with formation of the diazonium acetate, and its subsequent decomposition by polarised acetic acid or by the acetate anion; the naphthyl acetate formed is partly or wholly hydrolysed by the water formed in the reaction. That the reaction does not proceed *via* initial acetylation of the β-amino-group, followed by formation of a nitrosoacetonaphthalide and subsequent decomposition of its isomeric azo-form, is probably indicated by failure of the arylazo-β-acetonaphthalides to react with sodium nitrite and glacial acetic acid.

Experimental.

(1) *Preparation of Arylazo-β-naphthylamines.*—The general procedure is illustrated by the following example: A solution (or paste) of *p*-chloroaniline (12·75 g.; 0·1 g.-mol.) in hydrochloric acid (25 c.c., *d* 1·16) and water (20 c.c.) was diazotised below 5° with sodium nitrite (7 g.) dissolved in water (35 c.c.), and the filtered solution was stirred gradually into a solution (at 0°) of β-naphthylamine (14·3 g.) in alcohol (220 c.c.), to which fused sodium acetate had been added. After being stirred at 0° for 1 hour longer, the mixture was heated at 50° on the water-bath for 15 minutes and left overnight; the azo-compound had then separated in red crystals, which, recrystallised from glacial acetic acid, were obtained in scarlet prisms, m. p. 116° (Meldola and Forster, J., 1891, **59**, 690, give m. p. 116°).

Twenty-nine arylazo-β-naphthylamines were prepared similarly (see Table I), the only variation being that the toluidines, anisidines, and monohalogenoanilines were diazotised by the direct method (Saunders, " The Aromatic Diazo-Compounds," p. 3), and the halogenonitroamines and other less basic amines by the " inverted method " (Saunders, *op. cit.*, p. 9) or by the method of Hodgson and Walker (J., 1933, 1620). The yields of azo-compounds obtained by the last method were very good except in the case of *m*-fluorobenzeneazo-β-naphthylamine (30% yield), where a considerable amount of tarry matter was produced; this was avoided by adding sufficient alcohol, after coupling had taken place, to dissolve the products (including tar) at 65° and cooling the mixture very slowly.

(2) *Decomposition of Arylazo-β-naphthylamines by Sodium Nitrite and Glacial Acetic Acid.*—A solution of the azo-compound (3 g.) in hot glacial acetic acid (for quantities, see Table II; in some cases solution was not complete and a fine suspension was used) was treated at 70° with the calculated quantity of powdered sodium nitrite, added in portions with stirring, nitrogen being evolved. On completion of the reaction, the clear solution, which had been maintained at 65—70°, was kept for 48 hours at room temperature; the crystalline product was then collected and recrystallised. The filtrate, after dilution with ice to increase its volume fourfold, was kept at room temperature until the ice had melted and the precipitate (if any) was then collected (see below).

(3) *Identification.*—The chief products were (*a*) arylazo-β-naphthols, which were identified by comparison with authentic compounds obtained by coupling the requisite diazonium salts with β-naphthol, and (*b*) arylazo-β-naphthyl acetates, identified by comparison, after hydrolysis, with compounds (*a*) and also by comparison with compounds (*a*) which had been acetylated.

Hydrolysis. The acetyl compound (0·5 g.), dissolved as far as possible in 20—50 c.c. of alcohol containing hydrochloric acid (2 c.c., *d* 1·16), was refluxed for 30 minutes, the mixture cooled, made just alkaline with ammonia, and boiled for 2 minutes, and the arylazo-β-naphthol collected and recrystallised (usually from glacial acetic acid).

Acetylation. The arylazo-β-naphthol was refluxed for 24 hours with anhydrous sodium acetate (1 part) and acetic anhydride (20 parts). The cold solution was kept for 15 minutes, the sodium acetate removed, and the filtrate allowed to crystallise. The product was recrystallised from glacial acetic acid.

Examination of the tars produced in (2). The decomposition of those arylazo-β-naphthylamines named in Table I but omitted from Table II produced tars which could not be crystallised. The tar was collected and dissolved in hot alcohol, a little concentrated hydrochloric acid added, and the mixture refluxed for ½ hour. The cold solution deposited crystals, which were treated with aqueous ammonia. Recrystallisation

TABLE II.

Arylazo-β-naphthyl acetates.

The colour produced by concentrated sulphuric acid is given after the crystalline form.

Diazotised amine.	Acetic acid, c.c.	Sodium nitrite, g.	Product.	% Yield.	Crystalline form and solvent.	M. p.	% N found.	% N required.
m-Chloroaniline	30	0·75	m-*Chlorobenzeneazo-β-naphthyl acetate*	46·5	Small red needles, alcohol and glacial acetic acid (Violet-red)	81°	8·9	8·6
Aniline	100	0·9	*Benzeneazo-β-naphthyl acetate*	42·6	Red microscopic needles, glacial acetic acid (Violet-red)	117	9·8	9·6
p-Fluoroaniline	25	0·8	p-*Fluorobenzeneazo-β-naphthyl acetate*	43·0	Deep red needles, glacial acetic acid (Violet-red)	130	9·3	9·1
3-Nitro-*p*-toluidine	230	0·7	2-*Nitro-4-methylbenzeneazo-β-naphthyl acetate*	58·4	Red needles, alcohol (Violet-red)	133	12·0	12·0
p-Chloroaniline	40	0·75	p-*Chlorobenzeneazo-β-naphthyl acetate*	49·0	Deep red needles, alcohol (Violet-red)	134	8·7	8·6
p-Bromoaniline	34	0·65	p-*Bromobenzeneazo-β-naphthyl acetate*	44·0	Orange-red needles, alcohol (Violet-red)	136	7·8	7·6
4-Nitro-1-naphthylamine	250	0·62	4-*Nitronaphthaleneazo-β-naphthyl acetate*	56·3	Dark red-brown needles, glacial acetic acid (Dark violet-red)	155	10·9	10·9
2-Nitro-*p*-toluidine	230	0·7	3-*Nitro-4-methylbenzeneazo-β-naphthyl acetate*	73·7	Brown needles, glacial acetic acid (Violet-red)	157	12·2	12·0
4-Bromo-2-nitroaniline	300	0·57	4-*Bromo-2-nitrobenzeneazo-β-naphthyl acetate*	60·0	Fine carmine-red needles, alcohol (Red-violet)	160	10·3	10·2
m-Nitroaniline	210	0·72	m-*Nitrobenzeneazo-β-naphthyl acetate*	61·0	Red needles, glacial acetic acid (Violet-red)	162	12·9	12·6
4-Chloro-2-nitroaniline	300	0·65	4-*Chloro-2-nitrobenzeneazo-β-naphthyl acetate*	59·0	Fine carmine-red needles, glacial acetic acid (Red-violet)	163—164	11·5	11·4
4-Bromo-3-nitroaniline	200	0·57	4-*Bromo-3-nitrobenzeneazo-β-naphthyl acetate*	50·8	Orange needles, glacial acetic acid (Violet-red)	167	10·3	10·2
5-Nitro-1-naphthylamine	250	0·62	5-*Nitronaphthaleneazo-β-naphthyl acetate*	53·3	Carmine-red needles, glacial acetic acid (Red-violet)	180	10·9	10·9
Picramic acid	240	0·6	3 : 5-*Dinitro-2-hydroxybenzeneazo-β-naphthyl acetate*	77·5	Minute brownish-black needles, chlorobenzene (Red-violet)	184	14·5	14·2
p-Nitroaniline	300	0·72	*p*-Nitrobenzeneazo-β-naphthyl acetate	61·0	Red flattened needles, glacial acetic acid (Violet-red)	193 *	—	—
p-Aminobenzoic acid	220	0·74	p-*Carboxybenzeneazo-β-naphthyl acetate*	61·0	Red crystalline powder, glacial acetic acid (Red-violet)	206	8·6	8·4
o-Nitroaniline	175	0·72	*o*-Nitrobenzeneazo-β-naphthol	100	Orange-red needles, glacial acetic acid (Red-violet)	210 †	—	—
Anthranilic acid	120	0·74	*o*-Carboxybenzeneazo-β-naphthol	100	Red crystalline powder, glacial acetic acid (Violet-red)	276 ‡	—	—

* Meldola, East, J., 1888, **53**, 466, give m. p. 192—193°.
† Rowe, Levin, *J. Soc. Dyers and Col.*, 1924, **40**, 222, give m. p. 212°.
‡ *Idem*, *ibid.*, p. 222, give m. p. 276°.

of the product from glacial acetic acid or alcohol gave the arylazo-β-naphthol, identified by m. p. and mixed m. p., in almost quantitative yield.

Examination of the precipitates obtained by the addition of ice to the filtrates in (2). The addition of ice produced either a tar or a precipitate of indefinite m. p., which was probably a mixture of the arylazo-β-naphthol and its acetate, since, after hydrolysis with alcoholic hydrochloric acid, it gave the arylazo-β-naphthol.

The yield of arylazo-β-naphthol obtained from the precipitate (or tar), together with the amount of acetoxy-compound previously removed from the solution, corresponds almost quantitatively with the amount of arylazo-β-naphthylamine initially decomposed.

The authors thank Imperial Chemical Industries (Dyestuffs) Ltd. for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, July 24th*, 1941.]

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9. *Benzcyclooctatetraenes. Part II. The Action of Acetic Anhydride on δ-Benzylidenelævulic Acids.*

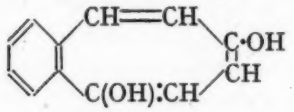
By W. S. RAPSON and R. G. SHUTTLEWORTH.

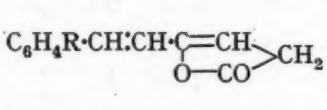
The dehydration products obtainable from δ-benzylidenelævulic acids by the action of acetic anhydride are shown to be almost certainly 2-*keto*-5-*styryl*-2 : 3-*dihydrofuran* derivatives and not 1 : 2-benz-$\Delta^{1:3}$-*cyclo*octadiene-5 : 8-diones as stated by Sen and Roy (*J. Indian Chem. Soc.*, 1930, **7**, 401). Benzoylation of these dehydration products by the Schotten–Baumann method yielded *dibenzoyl* derivatives, one benzoyl group being presumably linked to carbon. Attempts to obtain corresponding dibenzoyl derivatives from the Δ^1- and Δ^2-angelicalactones failed.

SEN and ROY (*loc. cit.*) prepared a number of coloured substances by the action of acetic anhydride on δ-benzylidenelævulic acid and its derivatives. They examined none of these coloured compounds in detail, but presumably because the product (A) from δ-benzylidenelævulic acid gave a dibenzoyl derivative in the Schotten–Baumann reaction with benzoyl chloride, they formulated this and all the analogous

compounds as 1 : 2-benz-$\Delta^{1:3}$-*cyclo*octadiene-5 : 8-diones, benzoylation of (A) being pictured as occurring through the corresponding dienolic structure (I).

We have submitted two of the substances described by Sen and Roy, namely, those from δ-benzylidenelævulic acid and δ-*p*-methoxybenzylidenelævulic acid, to further study and have found their reactions and properties much more in accord with their formulation as 2-*keto*-5-*styryl*-2 : 3-*dihydrofurans* (II, R = H and R = OMe respectively). In our view the dehydration of the δ-benzylidenelævulic acids

(I.) 

 (II.)

by acetic anhydride is to be compared with the dehydration of lævulic acid under analogous conditions to yield Δ^2-angelicalactone (Thiele, *Annalen*, 1901, **319**, 184). Thus oxidation of (A) with alkaline potassium permanganate yielded benzoic acid, and although its equivalent weight determination was made difficult because of its deep colour, it behaved more like a lactone than a di-enol. The lactonic behaviour was confirmed by its catalytic hydrogenation, four hydrogen atoms being taken up to yield a liquid product in which the lactonic function was not to be mistaken. The product from δ-*p*-methoxybenzylidenelævulic acid behaved in an exactly analogous manner.

In the light of these results it was expected that the product of the benzoylation of (A) by the Schotten–Baumann method, which was recorded as a dibenzoyl derivative by Sen and Roy (*loc. cit.*), would prove to be a monobenzoyl derivative of the enolic form of (II). Especially was this the case as the analytical figures for the two structures lie close together, and because the melting point of the product as reported by these workers was far below that of the purified material as handled by us. We have, however, been able to confirm Sen and Roy's characterisation of this substance as a dibenzoyl derivative by further analyses, as well as by the preparation of the analogous *di*-o-*chlorobenzoyl* and *di*-o-*iodobenzoyl* compounds. Since the dibenzoylated material gave no phthalic acid on oxidation, however, Sen and Roy's formulation of it must be in error, and it would appear as if one of the benzoyl groups is directly linked to carbon. No experimental evidence of this has been obtained, but benzoylation on carbon by the Schotten–Baumann method is not unknown (cf. *J. Amer. Chem. Soc.*, 1941, **63**, 1143). In this connection it is perhaps significant that the above products could not be obtained when pyridine was used in place of aqueous sodium hydroxide as condensing agent.

A *dibenzoyl* derivative of (II, R = OMe) is also described. No analogous compounds could be obtained, however, from the Δ^1- and Δ^2-angelicalactones by the Schotten–Baumann method.

Experimental.

δ-*Benzylidenelævulic Acid*.—The method of Erlenmeyer (*Ber.*, 1890, **23**, 74) was improved as follows: Benzaldehyde (41 c.c.), dissolved in alcohol (100 c.c.), was added simultaneously with 2N-sodium hydroxide (280 c.c.) to lævulic acid (42 c.c.). The mixture was shaken, placed in a boiling water-bath until homogeneous (8—10 mins.), and the solution then cooled rapidly by addition of ice. The crystals which separated on addition of dilute (1 : 1) hydrochloric acid (120 c.c.) were collected, dried by exposure to air, and recrystallised from benzene (3 vols.)–light petroleum (1 vol.). Yield, 32 g.

2-*Keto*-5-*styryl*-2 : 3-*dihydrofuran* (II, R = H).—The red product obtained from δ-benzylidenelævulic acid by the action of acetic anhydride was less contaminated by resinous materials, and the yield was very much improved, when the conditions used for its preparation by Sen and Roy (*loc. cit.*) were made rather less drastic. Acetyl chloride could not be substituted for acetic anhydride in the reaction. The acid (10 g.) was heated for 30 minutes in a boiling water-bath with acetic anhydride (20 g.). The red solid which remained after the reaction mixture had been stirred with an excess of saturated sodium bicarbonate solution was collected and recrystallised from methyl alcohol. The product (7·3 g., 80%) had m. p. 95·5° and not 196° as stated by the above authors. It was slowly soluble in sodium hydroxide solution, but addition of mineral acid to its solution so obtained yielded a viscous red oil which was not identical with the starting material, since it dissolved in sodium bicarbonate solution. Oxidised in the usual way with alkaline potassium permanganate, it yielded benzoic acid. Accurate values for the equivalent weight (found by solution in excess of sodium hydroxide and back-titration) were not possible on account of the deep red colour of the solution (Found : equiv., 197·2. Calc. for $C_{12}H_{10}O_2$: equiv., 186). The material was somewhat unstable on protracted storage in the light, being gradually converted into a pale brown, resinous substance of lower m. p. It was unchanged after being kept for a fortnight or longer, however, in a vacuum desiccator in the dark.

2-*Keto*-5-β-*phenylethyltetrahydrofuran*.—The above material, dissolved in alcohol, was treated with a palladium–strontium carbonate catalyst and shaken with hydrogen at 1—2 atms. The *product* was a faintly yellow liquid, b. p. 173—175°/7 mm., which could not be further hydrogenated (Found : C, 75·3; H, 7·5;

equiv. by back-titration, 187·8. $C_{12}H_{14}O_3$ requires C, 75·8; H, 7·4%; equiv., 190). It was insoluble in sodium bicarbonate solution, but soluble in aqueous sodium hydroxide. Addition of mineral acid to its solution in sodium hydroxide yielded an oil which, although immediately soluble in sodium bicarbonate solution, soon lost this solubility on standing.

Behaviour of 2-Keto-5-styryl-2 : 3-dihydrofuran in the Schotten–Baumann Reaction.—The material (3·7 g., 1 mol.) was treated in quick succession with benzoyl chloride (14 g., 5 mols.) and excess of 2N-sodium hydroxide (200 c.c.), and the flask vigorously shaken under running water. The *dibenzoyl* derivative crystallised almost immediately. When the smell of benzoyl chloride could no longer be detected, the aqueous solution was decanted, and the product washed several times with water by decantation and finally recrystallised from slightly aqueous acetone (charcoal). It formed fine yellow needles, m. p. 177·5—178·5° (Sen and Roy, *loc. cit.*, describe a light yellow powder, m. p. 160°) [Found: C, 79·2; H, 4·6; *M* (Rast), 390. $C_{26}H_{18}O_4$ requires C, 79·2; H, 4·6%; *M*, 394. Calc. for $C_{19}H_{14}O_3$: C, 78·6; H, 4·8%; *M*, 290]. Oxidised in the usual way with alkaline potassium permanganate, this dibenzoyl derivative yielded benzoic acid, and attempts to establish the simultaneous formation of phthalic acid failed. Benzoylation could not be effected by the use of pyridine as condensing agent.

When *o*-chlorobenzoyl chloride was used in the above reaction, the *di-o-chlorobenzoyl* derivative was obtained in brilliant yellow, flat, elongated prisms from aqueous acetone, m. p. 159·5—160° (Found: C, 67·2; H, 3·5. $C_{26}H_{16}O_4Cl_2$ requires C, 67·4; H, 3·5%. Calc. for $C_{19}H_{13}O_3Cl$: C, 70·3; H, 4·0%).

The *di-o-iodobenzoyl* derivative, obtained by an analogous procedure, formed small, yellow, transparent prisms of rhombohedral outline from slightly aqueous dioxan, m. p. 192—193° (Found: C, 48·3; H, 2·5. $C_{26}H_{16}O_4I_2$ requires C, 48·3; H, 2·5%. Calc. for $C_{19}H_{13}O_3I$: C, 54·8; H, 3·1%).

2-Keto-5-p-methoxystyryl-2 : 3-dihydrofuran (II, R = OMe).—This substance was obtained by a procedure analogous to that described above for the preparation of the corresponding benzylidene derivative. Recrystallised from methyl alcohol, it formed brick-red prisms, m. p. 115—115·5°, and not 78° as reported by Sen and Roy (*loc. cit.*) (Found: C, 72·2; H, 5·3. Calc. for $C_{13}H_{12}O_3$: C, 72·2; H, 5·6%). The material was unstable, and after exposure to light for as short a period as 24 hours, it had undergone considerable decomposition, sintering at 82° and forming a meniscus at 100°. It kept better in a vacuum desiccator in the dark. In other respects its properties agreed with those found for the above benzylidene derivative. It yielded with benzoyl chloride in the Schotten–Baumann reaction a *dibenzoyl* derivative, which formed lustrous, deep orange-coloured prisms from aqueous acetone, m. p. 170—171° (Found: C, 76·1; H, 4·9. $C_{27}H_{20}O_5$ requires C, 76·4; H, 4·7%. Calc. for $C_{20}H_{16}O_4$: C, 75·0; H, 5·0%). It gave anisic acid on oxidation in the usual way with alkaline potassium permanganate. When it was hydrogenated by a procedure analogous to that described above for the benzylidene derivative, *2-keto-5-β-p-methoxyphenylethyltetrahydrofuran* was produced as an oil, b. p. 195—200°/5 mm., soluble in aqueous sodium hydroxide, but insoluble in sodium bicarbonate solution (Found: equiv. by back-titration, 222. $C_{13}H_{16}O_3$ requires equiv., 220).

UNIVERSITY OF CAPE TOWN, SOUTH AFRICA. [*Received, August 5th*, 1941.]

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10. *Sapogenins. Part XII. The Position of the Carboxyl Group in Certain Triterpene Acids.*

By PHILIP BILHAM, GEORGE A. R. KON, and WALTER C. J. ROSS.

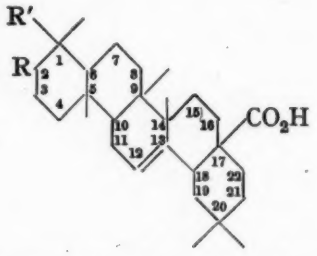
In continuation of previous work (Bilham and Kon, J., 1941, 552) it is shown that the abnormal behaviour of unimolecular films of hedraganic acid is not attributable to collapse, and the earlier findings are confirmed. Measurements on derivatives of β-boswellic, ursolic, and betulic acid, in which there are no polar groups apart from the carboxyl, support the conclusion that in these compounds also the polar group is attached to a terminal ring. The constitution of these triterpenes is discussed.

RECENT measurements on unimolecular films of hedraganic and the isomeric oleananic acids (Bilham and Kon, J., **1941**, 552) have shown that these occupy areas too small to be compatible with the formulation (I) originally due to Haworth (*Ann. Reports*, 1937, **34**, 337 *et seq.*) and later adopted by Ruzicka (compare, *e.g.*, Ruzicka, Cohen, Furter, and Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735, and subsequent papers). These results led to the suggestion (Bilham and Kon, *Nature*, 1941, **147**, 745; *loc. cit.*) that the carboxyl group in the acids of the oleanolic acid–hederagenin group of triterpenes occupies a position in ring E; on the assumption that the location of the other groups in the Haworth formula is correct, these acids are represented by the general structure (II).

The same method of investigation is now being extended to a comprehensive series of sapogenins and related triterpenes; as in our previous work, particular attention is devoted to compounds in which there

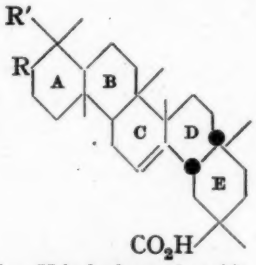
is only one polar group in the molecule, although the measurements are in some cases supplemented by observations on compounds having additional polar groups. The results obtained with hedraganic acid and with derivatives of β-boswellic, ursolic, and betulic acids are reported in the present communication.

(I.)



R = H in hedraganic and α- and β-oleananic acids;
= OH in oleanolic acid, gypsogenin, and hederagenin.

(II.)



R' = H in hedraganic acid;
= Me in oleanolic and oleananic acids;
= CHO in gypsogenin;
= CH_2·OH in hederagenin.

Materials.—In our previous communication it was stated that films of hedraganic acid behaved in an unusual manner, although the limiting areas observed were of the expected order of magnitude. To make certain that these results were not accidental, the acid used for the present investigation was prepared from hederagenin, which is much more readily obtained pure than the gypsogenin previously used; the properties of the acid were, however, identical with those of our earlier specimen.

In order to eliminate the hydroxyl group of β-boswellic acid, the methyl ester was oxidised to methyl β-boswellenonate or methyl β-boswellenedionate (Simpson and Williams, J., 1938, 1712). Both these esters undergo reduction by the Clemmensen method to the same beautifully crystalline *methyl β-boswellanate* (III, R = H). This ester is evidently very resistant to hydrolysis and is recovered unchanged after treatment which causes the complete hydrolysis of β- and γ-oleananic esters; since the ester gave a satisfactory film and only a small amount of material was available, the preparation of the acid was not deemed necessary.

Ursolic acid was isolated from bearberry (*Arctostaphylos Uva Ursi*) leaves by the method of van der Haar (*Rec. Trav. chim.*, 1924, **43**, 367), which we found to be greatly preferable to that of Sando (*J. Biol. Chem.*, 1931, **90**, 477); the same procedure is also very convenient for the isolation of oleanolic acid from cloves. Methyl ursonate was readily reduced to methyl ursanate by Clemmensen's method, but the acid obtained from this ester as described by Jacobs and Fleck (*J. Biol. Chem.*, 1931, **92**, 487) could not be induced to crystallise from any of the solvents tried; the specimen used in our measurements was purified by repeated precipitation of the crystalline sodium salt from an ethereal solution of the acid and acidification in presence of pure ether; it melted somewhat higher than the crystalline specimen described by Jacobs and Fleck and gave the same beautifully crystalline ester on treatment with diazomethane.

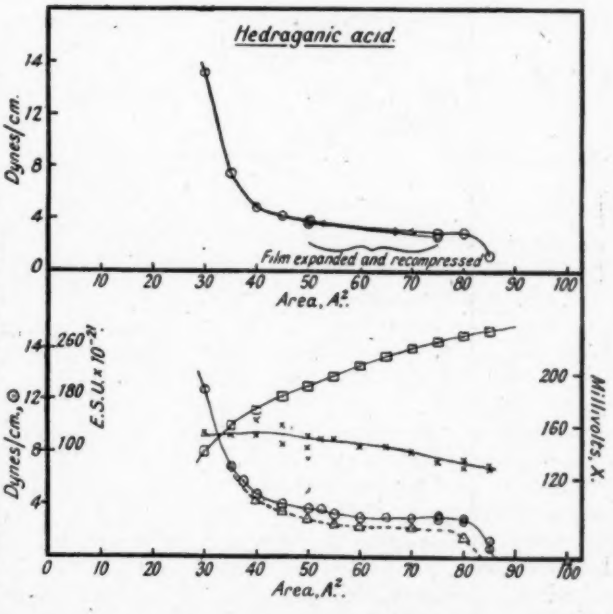
Betulic acid occurs in the bark of *Cornus Florida* L. (Owen, Robertson, and Soliman, J., 1939, 1269) and it has also been prepared from betulin (Ruzicka, Lamberton, and Christie, *Helv. Chim. Acta*, 1938, **21**, 1706). In order to obtain a derivative without the hydroxyl group in ring A, dihydrobetulonic acid was prepared from betulin (Ruzicka and Isler, *ibid.*, 1936, **19**, 506). Reduction of this acid with hydrazine and sodium ethoxide was unsuccessful, possibly owing to the separation of the very sparingly soluble sodium salt of dihydrobetulonic acid from the solution; the methyl ester was, however, easily reduced by Clemmensen's method to *methyl dihydrobetulanate*. This ester is exceptionally resistant to hydrolysis, although we have succeeded in preparing a small amount of the *acid* from it by drastic treatment. It was eventually found that the same acid can be easily prepared in excellent yield by the reduction of the keto-acid by Clemmensen's method; its identity was checked by reconversion into the methyl ester with diazomethane.

Results.—The measurements recorded in this communication were obtained by the methods used in our previous paper (*loc. cit.*). The results previously reported for hedraganic acid have been confirmed and subjected to tests designed to eliminate possible false effects due to the collapse or spontaneous contraction of the films. The lower curve (Fig. 1) shows the results obtained when films were spread at a large area and compressed to areas of 30—40 sq. A. and then re-expanded. Some hysteresis is evident, but as the film exhibits both spontaneous contraction and spontaneous "expansion," which phenomena tend to give high values for the surface pressure when compressing a film and low values

on expanding it in spite of protracted pauses between each shift of the barrier, the difference between the two curves is not significant. Further tests were made, a typical example of which is shown in the upper curve, where the film was compressed between 75 and 50 sq. A., re-expanded to 75 sq. A., and finally compressed to 50 sq. A. The readings were practically the same at each area. The film was then compressed to 30 sq. A. and followed the same course as films which had only been subjected to a single compression. Throughout these various experiments the surface potentials corresponded with the changes of area closely and were homogeneous over the surface.

The unusual type of curve obtained cannot therefore be attributed to collapse or spontaneous contraction, and must be caused by a rearrangement of the molecules in relation to the water surface. The first evidence of close packing of the molecules is obtained at an area of 86 sq. A., and a small but definite pressure of 3 dynes/cm. is required to reduce the area per molecule to 80 sq. A. Thereafter, the area may be reduced to a half of this value with a further increase of surface pressure of only 2 dynes/cm. During this compression the value of μ falls regularly. It is suggested that during the compression the molecules, which were much tilted when an ample area was available to each, are individually brought to a nearly vertical position, and that, having attained a pressure in the film sufficient to bring a few of them to the new orientation, no greater force, or very little more, is necessary to lift them all. When the rearrangement of all the molecules in the film is complete, the reduction of the area to 30 sq. A. needs a further increase in pressure of about 9 dynes/cm. This part of the curve gives the bulk compressibility of the molecule in the new position and is similar to that of the other carboxylic acids examined.

FIG. 1.



The behaviour of hedraganic acid is analogous to that of lupenediol and lupenetriol monoacetate (Bilham, Jones, and Meakins, J., 1941, 761), in which there is a second hydrophilic group which is at first attached to the water surface and leaves the water on compression. No such group is present in hedraganic acid, unless the double bond acts in this capacity. In any case, it is difficult to explain why this acid should behave differently from γ-oleananic acid, from which it differs solely by the absence of a methyl group in ring A, or at a point remote from the polar group and the double bond. The difference observed appears to suggest some more profound difference in the structure of these acids, and hence in that of the parent sapogenins, hederagenin and oleanolic acid, which does not find expression in the current formulæ of these compounds. A further difference is the failure of hedraganic acid to lose the carboxyl group on heating (Bilham and Kon, *loc. cit.*), which contrasts with the ready decarboxylation of β- and γ-oleananic acids and seems to suggest a difference in the immediate environment of the carboxyl group. For the present, these facts are placed on record until an explanation of them can be found.

Of the new compounds examined (see Fig. 2), methyl β-boswellanate gives a weak, solid film which withstands a pressure of only a few dynes/cm., but this is sufficient to determine the limiting value for the area, 51 sq. A.; the value of the surface potential at that area is 352 e.s.u. $\times 10^{-21}$.

Ursanic acid forms a strong, solid, moderately compressible film which shows spontaneous contraction. The area, 52 sq. A., is identical with that of β-oleananic acid and the compressibility of the film is also comparable. The value of μ is, however, much lower (94 e.s.u. $\times 10^{-21}$) and is comparable with that of a saturated acid, such as dihydrobetulanic acid (below). This may indicate that the double bond occupies a position remote from the carboxyl group, which must be situated in one of the end rings.

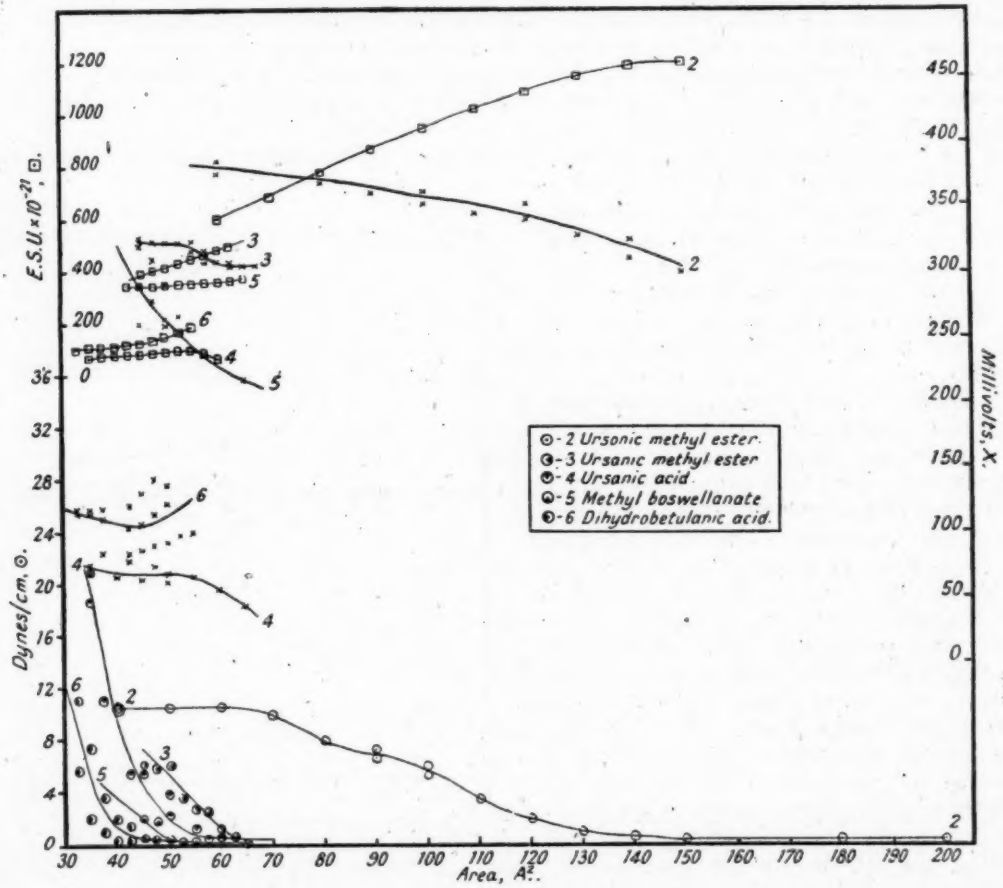
Methyl ursanate forms a weak, easily compressible film collapsing at 3 dynes/cm. and having an area of 62 sq. A.; the value of μ at this area is 550 e.s.u. $\times 10^{-21}$.

Methyl ursonate gives films like those of methyl oleanonate (Askew, J., 1936, 1585); these are

gaseous and lie flat, giving an area of 135 sq. A. with $\mu = 1174$ e.s.u. $\times 10^{-21}$. The films withstand a pressure of 10 dynes/cm. before collapsing at an area of about 75 sq. A., a behaviour pointing to the presence of two equally balanced hydrophilic groups at opposite ends of the molecule.

Dihydrobetulanic acid greatly resembles γ-oleananic acid in its behaviour, although it occupies an even smaller area, only 40 sq. A. The value of μ at this area is also lower, 113 e.s.u. $\times 10^{-21}$, as would be expected in a saturated acid. The behaviour of the dipole and the compressibility of the film are similar to those of γ-oleananic acid, but it is noteworthy that, whereas the ester of the latter acid forms a weak film which collapses at low pressures, methyl dihydrobetulanate fails to form a film altogether.

FIG. 2.



Discussion.—The minimum areas in sq. A. calculated from models for a hydropicene structure such as (I) and (II) with different positions of the polar group are given in the following table:

Polar group at	*cis*-.	Minimum.	*trans*-.	Polar group at	*cis*-.	Minimum.	*trans*-.
C_1	73(52)	72	99	C_{17}	77	—	—
C_3	99	82	43	C_{20}	79(45)	45	89(45)

The model used in the above measurements has the following configuration: rings A, B, and C of the "armchair" form with C modified by a double bond in position 12:13 and *trans*-junctions of A/B and B/C; rings D and E are boat-shaped with carbon atoms 13, 16, 19, and 22 uppermost and the angular methyl group on C_{17} pointing downwards; the junction D/E is *cis*, a configuration necessary to account for the reactions of quillaic and echinocystic acids (Bilham and Kon, *loc. cit.*; J., 1940, 1469).

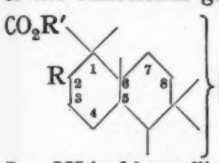
The figures in cols. 2 and 4 denote areas measured with the relevant bond vertical, which theoretically would be the preferred orientation; the figures in parentheses are obtained by orienting the molecule to occupy the minimum area possible with the polar group still touching the water surface, *i.e.*, theoretically, the area occupied when the film has been compressed to the collapsing point.

The figures in the third column denote, in general, some position intermediate between these two orientations, in which the vertical projection of the model has the least possible area.

The substitution of a five-membered ring E for a six-membered one makes but little difference; similarly the mode of junction of rings D and E and their configuration have but little influence on the area of a molecule oriented on a polar group at C_1 or C_2, although they are of great importance when the molecule is oriented on a polar group attached to ring E. It should be noted that the model chosen is only one of several possible arrangements and that although the junction D/E is *cis*, it does not represent the optimum configuration for the formation of lactones. The latter still presents a difficulty which has to be borne in mind; the optimum configuration from the point of view of lactonisation leads to calculated areas which are distinctly larger than those given above.

It will thus be seen that all the acids and esters examined up to the present give films having small areas, such as would be expected if the polar groups are attached to terminal rings.

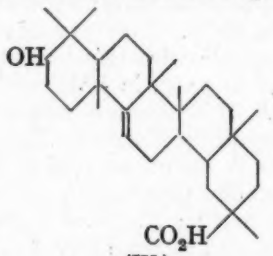
Of these compounds methyl β-boswellanate affords a useful standard of comparison. The position of the functional groups in the parent β-boswellic acid, apart from some uncertainty regarding the position of the double bond (see below), is known: it is a β-hydroxy-acid (Simpson and Williams, J., 1938, 686) and, since it has been converted into α-amyrin (Ruzicka and Wirz, *Helv. Chim. Acta*, 1939, **22**, 948), the hydroxyl group must be on C_2 and the carboxyl on C_1, as in the partial formula (III) (Simpson and Williams, J., 1938, 1712). The limiting area found for methyl β-boswellanate is in good agreement with this structure.



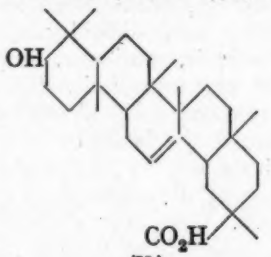
R = OH in β-boswellic acid;
= H in methyl β-boswellanate.

(III.)

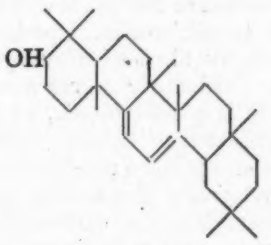
Ursolic acid is also an α-amyrin derivative (Goodson, J., 1938, 999), otherwise little is known of its chemistry. The similarity between this acid and oleanolic acid has already been noted (compare Dodge, *J. Amer. Chem. Soc.*, 1918, **40**, 1932; van der Haar, *loc. cit.*), and it is strikingly borne out by the surface film measurements now recorded; these clearly suggest that the carboxyl group of ursolic acid must occupy a position similar to that of oleanolic acid, in a terminal ring, and remote from the hydroxyl group. This receives striking support from the behaviour of methyl ursonate in forming gaseous films of large area similar to those of methyl oleanonate, and suggests that the functional groups of ursolic acid are disposed as in formulæ (IV) and (V):



(IV.)



(V.)



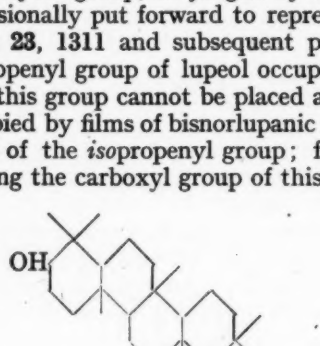
(VI.)

The position of the double bond of ursolic acid, as also in β-boswellic acid, is the same as that in α-amyrin. It has been suggested by Simpson and Williams (J., 1938, 1712) that the double bond of β-boswellic acid may be situated in ring B, between C_6 and C_7, or C_7 and C_8. Recent attempts to find support for this formulation were unsuccessful (Simpson and Kon, J., 1941, 793) and the reactions of α-amyrin suggest that this compound contains the grouping $>C{:}CH{\cdot}CH_2{\cdot}CH<$ in one ring (Spring and Vickerstaff, J., 1937, 249), a grouping also present in β-amyrin. Such a grouping is necessary to account for the formation of dehydro-compounds with two double bonds in one ring as in formula (VI), and it can only be accommodated in ring C in the triterpene skeleton current at the present time, as in (IV) and (V).

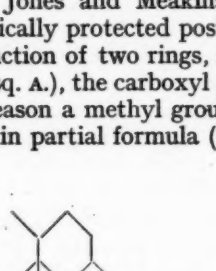
Of these two formulæ, (V) is that adopted for oleanolic acid, since it is necessary to account for the ready lactonisation of this and related compounds (compare Bilham and Kon, *loc. cit.*). Ursolic acid does not lactonise under comparable conditions, if at all (Winterstein and Stein, *Z. physiol. Chem.*, 1931, **202**, 217), and this would suggest the alternative formula (IV) for ursolic acid (such a formula, with alternative positions for the carboxyl group on C_{17} or C_{20}, has been discussed by Fujii and Oosumi, *J. Pharm. Soc. Japan.*, 1939, **59**, 264). It must, however, be borne in mind that the difference between ursolic and oleanolic acid and, hence, that between the amyrins, is not fully expressed by the formulæ (IV) and (V) because in that case the dehydro-compounds of type (VI) obtained from the amyrins should be the same, whereas they are distinct; there must therefore be some other

difference, such as a different mode of locking of two rings. A different mode of locking of rings D and E would be sufficient to give two acids of the formula (V), of which only one would be capable of lactonisation, although it is difficult to see how such a difference alone would suffice to account for the known differences in the reactions observed in the amyrins. For the present, formula (IV) may be adopted to represent ursolic acid, as expressing most of the known facts.

The carbon skeleton of the betulin group of triterpenes appears to be somewhat different from that of the amyrin group, as judged by their behaviour on dehydrogenation, and the formula (VII) has been provisionally put forward to represent these compounds (Ruzicka and Rosenkranz, *Helv. Chim. Acta*, **1940, 23,** 1311 and subsequent papers). Jones and Meakins (J., **1941, 757**) have found that the *iso*propenyl group of lupeol occupies a sterically protected position. Surface film measurements show that this group cannot be placed at the junction of two rings, and as C_{17}, on account of the small area occupied by films of bisnorlupanic acid (48 sq. A.), the carboxyl group of which is formed by the degradation of the *iso*propenyl group; for this reason a methyl group must be attached to the carbon atom bearing the carboxyl group of this acid, as in partial formula (VIII):

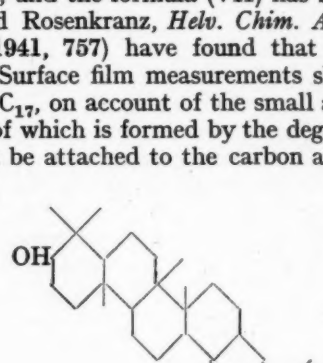


(VII.)



R = Me in lupeol;
= CH_2·OH in betulin;
= CO_2H in betulic acid.

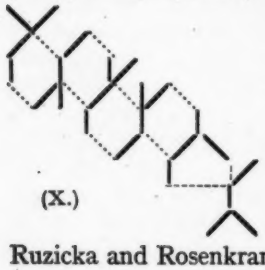
(VIII.)



(IX.)

The primary carbinol grouping of betulin occupies the place of one methyl group of lupeol (Ruzicka and Brenner, *Helv. Chim. Acta*, **1939, 22,** 1523) and it must be placed so as to account for the ready lactonisation of betulic acid (Owen, Robertson, and Soliman, *loc. cit.*) and the well-known cyclisation of betulin to *allo*betulin, a process presenting some difficulty with formula (VII). The very small area occupied by films of dihydrobetulanic acid is, moreover, quite incompatible with this formula, but finds a satisfactory representation in the new formulation (IX) now put forward, in which the polar group R is placed on C_{20} as in the triterpene acids already discussed. This accounts naturally for the cyclisation of betulin derivatives, whilst the inability of methyl dihydrobetulanate to form films and its exceptional resistance to hydrolysis find a reasonable explanation in the presence of the bulky *iso*propyl group (formed by the reduction of the *iso*propenyl group originally present) on the carbon atom carrying the carbomethoxyl group. The only difficulty arising out of the new formula is presented by the two dicarboxylic acids, A and E, of Ruzicka, Lamberton, and Christie (*loc. cit.*), which are formed by the oxidation of betulic acid, since it is the C_{28} acid, a malonic acid according to the new formulation, which appears to form an anhydride; this has not, however, been obtained crystalline.

It may seem remarkable that the limiting area found for dihydrobetulanic acid, $C_{25}H_{42}{>}CPr^{\beta}{\cdot}CO_2H$, is somewhat smaller than that of bisnorlupanic acid, $C_{25}H_{42}{>}CMe{\cdot}CO_2H$, but reference to formulæ (VIII) and (IX) shows that a difference is to be expected because the carboxyl group of bisnorlupanic acid represents the *iso*propyl, and not the carboxyl, group of dihydrobetulanic acid; the two acids thus represent the two possible stereochemical arrangements discussed on p. 38.



(X.)

No finality is claimed for the allocation of the angular methyl groups in formula (IX), which is merely a modification of the structure tentatively put forward by Ruzicka and Rosenkranz; the particular arrangement was chosen because it is divisible into *iso*prene units as shown in formula (X) and, incidentally, appears to offer a better explanation of the formation of sapotalene and 2 : 7-dimethylnaphthalene by the dehydrogenation of betulin (compare Ruzicka and Rosenkranz, *loc. cit.*) than formula (VII).

Experimental.

(M. p.'s are uncorrected; unless otherwise stated, analysis specimens were dried for 2 hours at 100°/1—2 mm.)

Hedraganic Acid.—Hederagenin was prepared from soap-nut saponin supplied by Messrs. Boake, Roberts & Co. Ltd., of Stratford, E.15, by the method of Winterstein and Meyer (*Z. physiol. Chem.*, 1931, **199**, 37); it was esterified with diazomethane, and the ester oxidised with copper bronze to hedragonic ester (Tsuda and Kitagawa, *Ber.*, 1938, **71**, 1604). The preparation of hedraganic acid from this was carried out as described in our previous paper (*loc. cit.*).

Methyl β-Boswellanate.—500 Mg. of methyl β-boswellate, prepared from β-boswellic acid of high rotation (Simpson and Williams, J., 1938, 1712; compare Simpson and Kon, *loc. cit.*), were oxidised exactly as described by Simpson and Williams (*loc. cit.*); the product solidified on rubbing with methyl alcohol, and was dissolved in ether–methyl alcohol, the ether being then evaporated off. A small amount of solid separated on cooling; it sintered at 150° but did not melt completely until 210°. On being kept overnight, the filtrate deposited a second and much larger crop of crystals (total 300 mg.), m. p. 248°, evidently consisting of methyl boswellenedionate. The pure monoketo-ester was obtained when 600 mg. of methyl β-boswellate in 120 c.c. of acetic acid and 12 c.c. of water were kept at room temperature while a solution of 240 mg. of chromium trioxide in 2·4 c.c. of water and 12 c.c. of acetic acid was gradually dropped in; the ester isolated as before (300 mg.) had m. p. 160° after one crystallisation from methyl alcohol.

300 Mg. of methyl boswellenedionate were boiled for ½ hour with 16 c.c. of acetic acid, 4 c.c. of hydrochloric acid, and 6 g. of amalgamated zinc shavings. The product isolated by dilution and extraction with ether (180 mg.) was dissolved in 25 c.c of petroleum (b. p. 40—60°), and the solution allowed to percolate through a short column of activated alumina, the ester being completely adsorbed. After washing with a further 50 c.c. of petroleum, the adsorbed ester was eluted with ether and recrystallised from methyl alcohol, in which it is much less soluble than the parent ketonic ester. The same material was also obtained by a similar reduction of methyl boswellenonate. It formed fine needles, m. p. 166—167°, $[\alpha]_D$ + 131·3° (c = 1·035 in chloroform) (Found: C, 81·9; H, 11·2. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·1%). 160 Mg. of the *ester* were heated in a sealed tube with 4 g. of potassium hydroxide in 3 c.c. of water and 17 c.c. of alcohol for 5 hours in an oil-bath kept at 165—170°; the ester was recovered unchanged.

Ursolic Acid.—Finely powdered bearberry leaves (660 g.) were left to stand for several days with 56 g. of potassium hydroxide (or 40 g. of sodium hydroxide) in 3·5 l. of alcohol. The filtered solution was acidified with hydrochloric acid and concentrated to a third of its volume, left overnight, and the precipitate of crude ursolic acid collected and washed first with a little alcohol, then thoroughly freed from inorganic material by washing with water; the procedure up to this point is that followed by van der Haar and by Dodge (*locc. cit.*), except that the latter used methyl alcohol as a solvent. The crystallisation of the crude acid so obtained presents considerable difficulty, as it tends to separate from solvents in a gelatinous form. The following simplified method was therefore adopted; the crude acid was dissolved in ether, and the strongly coloured solution shaken with 10% sodium hydroxide. This extracted much coloured impurity, but contained practically none of the sodium ursolate, which collected at the interface between the liquids. The aqueous layer was discarded, and the ethereal layer decanted off as completely as possible; the solid was once more shaken with ether and a little sodium hydroxide solution, the ether again decanted off, and the salt warmed on the steam-bath with a little sodium hydroxide solution to expel the remainder of the ether, whereupon it gradually became crystalline; it was filtered off, and washed with sodium hydroxide and then with water. The salt was dissolved in the minimum amount of alcohol, and excess of acetic acid added to the boiling solution; on seeding, ursolic acid crystallised in long needles, m. p. 276—277°.

Methyl Ursanate.—Ursolic acid was esterified with diazomethane, and the ester oxidised without further purification, giving a 75% yield of methyl ursonate, m. p. 188—190° after crystallisation from methyl alcohol (Jacobs and Fleck, *loc. cit.*, give m. p. 192—193°). The reduction was carried out as described above, giving an excellent yield of methyl ursanate, m. p. 117—118°, in agreement with Jacobs and Fleck (*loc. cit.*), $[\alpha]_D$ + 99·7° (c = 1·445 in pyridine).

Ursanic Acid.—Methyl ursanate was hydrolysed in a sealed tube as described above, and the acid purified by two precipitations from the sodium salt, which was crystalline. It could not be made to crystallise from any of the solvents tried; it was dried for 2 hours at 100° and a further 3 hours at 130°/0·5 mm., and melted at 228—230° (Jacobs and Fleck found m. p. 223—225°) (Found: C, 81·9; H, 10·7. Calc.: C, 81·8; H, 11·0%). An attempt to prepare the acid by the reduction of methyl ursonate by the Kishner–Wolff method was unsuccessful; the acidic portion of the reaction product melted at 275—280° and could not be crystallised. On re-esterification with diazomethane, it gave a mixture, from which methyl ursonate, m. p. 184°, was isolated, so the reduction had evidently been incomplete.

Betulin.—Betulin was isolated from birch bark by extraction with benzene (Ruzicka and Isler, *loc. cit.*); as the purification proved somewhat troublesome, crude betulin was acetylated, and the diacetate freed from amorphous, coloured impurities by percolating a solution in benzene–petroleum (1 : 1) through a column of alumina. The recovered material was pure after one crystallisation from alcohol.

Methyl Dihydrobetulanate.—Dihydrobetulonic acid was prepared and purified as described by Ruzicka and Isler (*loc. cit.*), the yields quoted by these authors being reproduced without difficulty; the acid had m. p. 263°, and the methyl ester prepared from it and twice crystallised from methyl alcohol, m. p. 189°. This was reduced exactly as described above; the *ester* crystallised from methyl alcohol, in which it is much

less soluble than the parent ketonic ester, in needles, m. p. 166—167° (Found: C, 81·8; H, 11·5. $C_{31}H_{52}O_2$ requires C, 81·5; H, 11·5%).

Hydrolysis. The ester was recovered unchanged after 4 hours' heating with 20% potassium hydroxide at 160—170°. When 100 mg. of ester were heated in a sealed tube with 10 c.c. of 10% alcoholic potassium hydroxide for 24 hours to 180°, most of the ester remained unchanged, but some 3 mg. of acid were isolated. The recovered ester was further treated with 20% potassium hydroxide, but again the greater part escaped hydrolysis.

Dihydrobetulanic Acid.—1 G. of dihydrobetulonic acid was heated in a sealed tube with 4·5 c.c. of 50% hydrazine hydrate and 25 c.c. of 5% sodium ethoxide for 16 hours to 200°. The acid recovered on acidification and extraction with ether proved to be unchanged, m. p. 263° (Found: C, 78·3, 78·3; H, 10·5, 10·9. Calc.: C, 78·6; H, 10·6%). The acid was then reduced by Clemmensen's method as described on p. 41; the reaction appeared to be complete after some 5 minutes' boiling, and the sparingly soluble *dihydrobetulanic* acid separated completely from the boiling solution; the yield was quantitative. The acid was crystallised first from acetic acid and later from acetone, and formed leaflets, m. p. 293° (Found: C, 81·5; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). It formed the ester, m. p. and mixed m. p. 166—167°, on treatment with diazomethane.

The authors' thanks are due to the Royal Society for a grant, and to Dr. J. C. E. Simpson for a specimen of acetyl-β-boswellic acid.

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11. *Carboxylic Acid Derivatives of* 4 : 4′-*Diaminodiphenylsulphone.*

By W. H. GRAY and B. C. PLATT.

The object of this work was the preparation of a series of carboxylic acid derivatives of 4 : 4′-diaminodiphenylsulphone by insertion of dicarboxylic acid side-chains into the amino-groups. Some of these retain the chemotherapeutic activity of the sulphone, and yield injectable soluble salts. The corresponding cyclic imides were also obtained, and yielded the carboxylic acids on mild hydrolysis.

THE isolation of 4 : 4′-diaminodiphenylsulphone as a by-product in the modern process of manufacture of *p*-aminobenzenesulphonamide led to the observation that the sulphone is much the more effective of the two in experimental pneumococcus infections (Buttle, Stephenson, Smith, Dewing, and Foster, *Lancet*, 1937, i, 1331), but its rather marked toxicity, and its insolubility over the range of p_H permissible for injection, make it unsuitable for clinical use. Certain Schiff's bases have considerably lower toxicity and unimpaired curative action (Wellcome Foundation, Ltd., Henry, and Gray, B.P. 419,265); ready solubility is attained when the sulphone is converted into monoamides of dicarboxylic acids, which form salts of low toxicity and useful pharmacological activity.

Several methods were used in preparing these amides. Those of the higher aliphatic dibasic acids were not obtained by heating the acid and the sulphone together; mixtures of products resulted, which could not be separated. This is probably to be attributed to prior formation of the acid anhydrides, since it has been shown by Carothers and co-workers (*J. Amer. Chem. Soc.*, 1933, **55**, 5023) that adipic anhydride and higher homologues are polymers with molecular weights of 3000 to 5000, and react with bases to give mixtures of products. A similar difficulty was experienced when the anhydrides themselves were employed. At the temperatures here used, also, the mixtures may be complicated by the presence of the imides; from succinic anhydride, which is monomeric, a mixture of amide (I; $n = 2$) and imide (II) was formed.

(I.) $SO_2(C_6H_4{\cdot}NH{\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2H)_2$ $\qquad$ $SO_2\left(C_6H_4{\cdot}N\begin{matrix}CO{-}CH_2\\CO{-}CH_2\end{matrix}\right)_2$ (II).

(III.) $C_6H_4\begin{matrix}CO\\CO\end{matrix}N{\cdot}C_6H_4{\cdot}SO_2{\cdot}C_6H_4{\cdot}NH_2$ $\qquad$ $SO_2\left(C_6H_4{\cdot}N\begin{matrix}CO\\CO\end{matrix}C_6H_4\right)_2$ (IV.)

(V.) $HO_2C{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}C_6H_4{\cdot}NH_2$

(VI.) $SO_2(C_6H_4{\cdot}NH{\cdot}CO{\cdot}C_6H_4{\cdot}CO_2H)_2$ $\qquad$ $C_6H_4\begin{matrix}CO{\cdot}NH{\cdot}C_6H_4\\CO{\cdot}NH{\cdot}C_6H_4\end{matrix}SO_2$ (VII.)

From phthalic anhydride, the mono- and the bis-imide (III and IV) were obtained in good yield by heating the requisite molecular proportion with the sulphone. By hydrolysis with aqueous alkali one of

the imide rings is opened, and the other broken off to leave the original amino-group, so that the monoimide (III) and the bisimide (IV) under these conditions both yield the monoamide (V). By milder hydrolysis, (IV) gives the bisamide (VI). The imides were also obtained by heating the sulphone with acid or neutral phthalic esters. (III) gives a diazo-reaction and so cannot have the alternative structure (VII); it is precipitated unchanged from hydrochloric acid solution on dilution with water, showing that the amino-group does not arise through hydrolysis during the test.

Partial hydrolysis, on the same lines, of 4 : 4′-*biscarbethoxyformamidodiphenylsulphone*, made by heating with ethyl oxalate, gave the analogous mono- and bis-carboxyformamido-derivatives. Esters of the higher aliphatic dibasic acids, like the anhydrides, gave products difficult to purify, and their amides were best prepared by the action of the ester chlorides upon the sulphone in presence of acid-binding agents.

Camphoric anhydride reacted more slowly than phthalic anhydride; in this case the bisimide was isolated. Similar reactions appear to occur with pimelic, maleic, malic, mucic, glutamic, and quinolinic acids, and the products are being investigated.

The toxicity and protective action of the compounds have been tested on mice by Dr. Stephenson of the Wellcome Physiological Research Laboratories, and the results are shown in the table. In streptococcal infections the activity is expressed in terms of that of *p*-aminobenzenesulphonamide, or for Nos. 5 and 8 of disodium *p*-(γ-phenylpropylamino)benzenesulphonamide αγ-disulphonate; in pneumococcal and staphylococcal infections of 2-(*p*-aminobenzenesulphonamido)pyridine; Nos. 1—4 and 8—12 were administered in 100 mg. doses to uninfected mice and caused no toxic symptoms.

No.	Name.	Activity in infections due to Streptococci.	Pneumococci.	Staphylococci.
1	4-Amino-4′-carboxyformamidodiphenylsulphone	0·1	0·34	10 mg. inactive
2	4 : 4′-Biscarbethoxyformamidodiphenylsulphone	1·0	trace	trace
3	4 : 4′-Biscarboxyformamidodiphenylsulphone	1·0	1·0	10 mg. inactive
4	4 : 4′-Biscarboxyacetamidodiphenylsulphone	0·1	0·1	—
5	4 : 4′-Bis-β-carboxypropionamidodiphenylsulphone	1·0	—	—
6	4 : 4′-Bis-succinimidodiphenylsulphone	trace	—	—
7	4 : 4′-Bis-δ-carbethoxyvaleramidodiphenylsulphone	somewhat <1	—	—
8	Disodium bis-δ-carboxyvaleramidodiphenylsulphone	5·0	1·0	—
9	4-Amino-4′-phthalimidodiphenylsulphone	inactive	inactive	inactive
10	4 : 4′-Bisphthalimidodiphenylsulphone	〃	〃	〃
11	4-Amino-4′-*o*-carboxybenzamidodiphenylsulphone	1·0	0·1—0·3	0·1
12	4 : 4′-Bis-*o*-carboxybenzamidodiphenylsulphone	0·01	trace	10 mg. inactive

Experimental.

4-*Amino*-4′-*carboxyformamidodiphenylsulphone.*—4 : 4′-Biscarbethoxyformamidodiphenylsulphone (8·0 g.) was added to 2·5% sodium hydroxide solution (87 c.c.) and heated over a gauze. After 6 minutes, when solution was complete, water (300 c.c.) was added, and the whole immediately cooled, since heating for a longer time gave rise to a precipitate of 4 : 4′-diaminodiphenylsulphone. The solution, filtered from a trace of insoluble matter, was acidified with dilute hydrochloric acid; the precipitated solid was ground with 10% hydrochloric acid (100 c.c.), washed with water, dried, and twice crystallised from aqueous acetone, yielding the *amino-acid* (4 g.), which frothed at 195° (Found: C, 51·5; H, 3·7; N, 8·7; S, 10·1. $C_{14}H_{12}O_5N_2S$ requires C, 52·5; H, 3·8; N, 8·7; S, 10·0%).

4 : 4′-*Biscarbethoxyformamidodiphenylsulphone.*—4 : 4′-Diaminodiphenylsulphone (7·5 g.; 1 mol.) and ethyl oxalate (17·5 g.; 4 mols.) were refluxed for 1½ hours, by which time the whole was practically solid. The cooled mass was ground and washed successively with ether, 10% hydrochloric acid (60 c.c.), and water; the product (11·7 g.), thrice crystallised from aqueous dioxan, yielded the 4 : 4′-*bis-ethyl* ester, m. p. 257° (Found: C, 53·6; H, 4·7; N, 6·4; S, 6·8. $C_{20}H_{20}O_8N_2S$ requires C, 53·5; H, 4·5; N, 6·2; S, 7·1%).

4 : 4′-*Biscarboxyformamidodiphenylsulphone.*—4 : 4′-Biscarbethoxyformamidodiphenylsulphone (16·5 g.) was added to ethyl-alcoholic potassium hydroxide (1240 c.c. of 0·5%); the solid dissolved and a precipitate immediately appeared. To ensure complete reaction, the whole was heated for 15 minutes on the water-bath. After cooling, the precipitate was collected, washed with alcohol, and extracted with cold water (1250 c.c.). The filtered aqueous solution was acidified with dilute hydrochloric acid to yield a white precipitate, which, after two recrystallisations from 50% aqueous acetic acid, gave the pure *bis-acid* (7·6 g.). This frothed at 188° to a solid, m. p. 275° (approx.) (Found: C, 49·6; H, 3·5; N, 7·3; S, 7·8. $C_{16}H_{12}O_8N_2S$ requires C, 49·0; H, 3·1; N, 7·1; S, 8·1%).

4 : 4′-*Biscarboxyacetamidodiphenylsulphone.*—Crude malonyl chloride (25 g., from 40 g. of malonic acid), dissolved in cold dioxan (40 c.c.), was slowly run into a solution of 4 : 4′-diaminodiphenylsulphone (20 g.) in dioxan (250 c.c.) at 65°. A bulky yellow precipitate formed during the addition, which was completed in ½ hour. After standing overnight, the precipitate was collected, washed with cold water, triturated with 10% hydrochloric acid (100 c.c.), and finally washed with water. The crude product was extracted with boiling water (1 l.); the filtrate, on cooling, deposited colourless needles of the *bis-acid* containing one molecule of

water of crystallisation (4·6 g.) (Found : C, 50·1; H, 4·25; N, 6·8; S, 7·2; equiv., by titration with NaOH, 225. $C_{18}H_{16}O_8N_2S,H_2O$ requires C, 49·4; H, 4·1; N, 6·4; S, 7·3%; equiv., 219). The crystals frothed at 183° with evolution of carbon dioxide to give 4 : 4′-bisacetamidodiphenylsulphone, m. p. 278° (Fromm and Wittmann, *Ber.*, 1908, **41**, 2270, give m. p. 280°).

4 : 4′-*Bis*-β-*carboxypropionamidodiphenylsulphone*.—An intimate mixture of 4 : 4′-diaminodiphenylsulphone (1·24 g.; 1 mol.) and freshly crystallised succinic anhydride (1 g.; 2 mols.) was heated at 170° for 3 hours, and the product extracted with boiling alcohol. A small insoluble portion (0·07 g.), which proved to be the imide (see below), was removed. Yield 1·62 g., sparingly soluble in water or acetone, m. p. 227°, resolidifying and remelting at the m. p. of the imide (Found : C, 53·6; H, 4·6; N, 6·3; S, 7·5. $C_{20}H_{20}O_8N_2S$ requires C, 53·6; H, 4·5; N, 6·3; S, 7·15%).

4 : 4′-*Bis-succinimidodiphenylsulphone*.—4 : 4′-Diaminodiphenylsulphone (1·24 g.) and succinic anhydride (1 g.) were heated together at 225° for 2 hours. The product was finely ground and shaken with acetone until the m. p. became constant; yield 1·35 g., insoluble in water, chloroform, and cold dilute alkali, m. p. 343° (Found : C, 58·5; H, 4·0; N, 6·8; S, 7·8. $C_{20}H_{16}O_6N_2S$ requires, C 58·3; H, 3·9; N, 6·8; S, 7·8%).

4 : 4′-*Bis*-δ-*carbethoxyvaleramidodiphenylsulphone*.—δ-Carbethoxyvaleryl chloride (21 c.c.) was added gradually with continuous stirring to 4 : 4′-diaminodiphenylsulphone (13·6 g.) dissolved in acetone (70 c.c.) containing precipitated calcium carbonate (10·9 g.) in suspension, and the mixture heated on the water-bath under reflux for 1½ hours. The acetone was removed under diminished pressure, and the oily residue macerated with cold water until crisp and recrystallised from acetone; yield 10·1 g., m. p. 139° (Found : C, 60·0; H, 6·4; N, 5·2. $C_{28}H_{36}O_8N_2S$ requires C, 60·0; H, 6·5; N, 5·0%). This was hydrolysed to the sodium salt of the free acid, for pharmacological testing, in the same way as the azelayl derivative (below).

4 : 4′-*Bis*-η-*carbomethoxyoctamidodiphenylsulphone*.—4 : 4′-Diaminodiphenylsulphone (4·2 g.) dissolved in acetone (22 c.c.) containing calcium carbonate (3·4 g.) in suspension, was treated gradually with η-carbomethoxyoctoyl chloride (7·4 g.), and the mixture heated under reflux for 2 hours. It was worked up in the same way as the adipic derivative; yield of first crop, 3·7 g., m. p. 122° (Found : C, 62·2; H, 7·2; N, 5·1; S, 5·2. $C_{32}H_{44}O_8N_2S$ requires C, 62·3; H, 7·2; N, 4·5; S, 5·2%).

4 : 4′-*Bis*-η-*carboxyoctamidodiphenylsulphone*.—4 : 4′-Bis-η-carbomethoxyoctamidodiphenylsulphone (1 g.) was heated on the water-bath under reflux with N-sodium hydroxide (3·25 c.c.) for several hours. The solution was filtered from a trace of unchanged ester, cooled in ice, and acidified slightly with dilute hydrochloric acid. The precipitated *acid* (0·6 g.) was dissolved in alcohol, the solution cooled in ice, and water added gradually with continual stirring; yield 0·44 g., m. p. 134° (Found : C, 61·1; H, 6·9; N, 4·9; S, 5·5. $C_{30}H_{40}O_8N_2S$ requires C, 61·2; H, 6·9; N, 4·8; S, 5·5%).

4-*Amino*-4′-*phthalimidodiphenylsulphone*.—(*a*) Phthalic anhydride (4·5 g.; 1 mol.) was added to a solution of 4 : 4′-diaminodiphenylsulphone (7·5 g.; 1 mol.) in pyridine (5·0 g.). The whole, heated for 1½ hours on the water-bath, became solid. After cooling, the product was ground with 10% hydrochloric acid (100 c.c.), and the insoluble portion collected, washed with water, dried, and thrice crystallised from dioxan, giving a white product (7·4 g.), m. p. 256—258° (Found : C, 63·3; H, 3·9; N, 8·0; S, 8·5. $C_{20}H_{14}O_4N_2S$ requires C, 63·3; H, 3·7; N, 7·4; S, 8·5%).

(*b*) 4 : 4′-Diaminodiphenylsulphone (7·5 g.) and phthalic anhydride (4·5 g.; 1 mol.), finely ground and intimately mixed, were heated at 200° for several hours, 10·7 g. of the same imide being obtained almost pure, m. p. 258—261°; after one recrystallisation from dioxan it melted at 262°.

(*c*) 4 : 4′-Diaminodiphenylsulphone (2·5 g.; 1 mol.), methyl hydrogen phthalate (1·8 g.; 1 mol.), and anhydrous zinc chloride (0·3 g.) were heated on the water-bath for 4 hours. The cooled mass was treated as in (*a*) to yield the required product.

(*d*) 4 : 4′-Diaminodiphenylsulphone (2·5 g.; 1 mol.) was heated with methyl hydrogen phthalate (3·6 g.; 2 mols.) for 5 hours on the steam-bath, and the cooled product treated as in (*a*) to give the pure *mono-imide* (3·0 g.).

4 : 4′-*Bisphthalimidodiphenylsulphone*.—(*a*) 4 : 4′-Diaminodiphenylsulphone (7·6 g.; 1 mol.) was heated for 2 hours on the steam-bath with a solution of phthalic anhydride (9·0 g.; 2 mols.) in pyridine (6 g.). The cooled mass was treated as in (*a*) above and the *bis-imide* (3·7 g.), m. p. 310°, was obtained after crystallisation from ethylene chlorohydrin (Found : C, 66·1; H, 3·2; N, 5·4; S, 6·3. $C_{28}H_{16}O_6N_2S$ requires C, 66·1; H, 3·2; N, 5·5; S, 6·3%).

A better yield was obtained by heating 4 : 4′-diaminodiphenylsulphone (7·6 g.; 1 mol.), phthalic anhydride (9·0 g.; 2 mols.), and pyridine (21 g.) under reflux for 1 hour. The bis-imide (12·3 g.), m. p. 311—313°, was obtained by treating the product as above.

(*b*) 4 : 4′-Diaminodiphenylsulphone (1·2 g.; 1 mol.) was heated with methyl hydrogen phthalate (3·6 g.; 4 mols.) for 6½ hours at 100°, followed by 3 hours' heating at 190—205°. The cooled melt was ground with 10% hydrochloric acid (30 c.c.); the insoluble portion was washed, dried, and recrystallised from ethylene chlorohydrin to yield the bis-imide (1·5 g.), m. p. 313—315°.

Boiling 50% acetic acid or N/2-sodium acetate had no effect on the bis-imide.

(*c*) 4 : 4′-Diaminodiphenylsulphone (14·9 g.) and ethyl phthalate (23·6 c.c.; 2 mols.) were boiled for 5 hours, the alcohol formed being distilled off through a downward condenser. The solid product obtained was

extracted with boiling acetone–alcohol (1 : 1), and the insoluble portion crystallised from pyridine (55 c.c.) and then from ethylene chlorohydrin (140 c.c.); yield, 16·7 g. (Found : C 66·2; H, 3·4; N, 5·5; S, 6·1%).

4-Amino-4′-o-carboxybenzamidodiphenylsulphone.—(*a*) 4-Amino-4′-phthalimidodiphenylsulphone (4·6 g.) was heated for 25 minutes on the steam-bath with 5% aqueous sodium hydroxide (115 c.c.). The resultant clear solution was cooled, diluted with water (250 c.c.), and acidified with dilute hydrochloric acid. The precipitate was dissolved in 2% aqueous sodium hydroxide, decolourised with charcoal, and reprecipitated from the cold clear solution with dilute mineral acid. The dried precipitate was *4-amino-4′-o-carboxybenzamidodiphenylsulphone* (3·0 g.) (Found : C, 60·4; H, 4·0; N, 7·3; S, 7·7; equiv. by titration with NaOH, 391. $C_{20}H_{16}O_5N_2S$ requires C, 60·6; H, 4·1; N, 7·1; S, 8·1%; equiv., 396).

The solid frothed at 176° to a liquid, which on continued heating resolidified to give the monoimide. The latter is also obtained by prolonged treatment of the former with boiling water.

(*b*) 4 : 4′-Bisphthalimidodiphenylsulphone (0·5 g.) was boiled for 20 minutes with N/10-sodium hydroxide (60 c.c.); the resultant clear solution was, after cooling, acidified with dilute hydrochloric acid to yield the amino-acid (0·4 g.).

On very slow heating of 4-amino-4′-*o*-carboxybenzamidodiphenylsulphone, no frothing was observable and melting occurred at 248—250°, *i.e.*, at the m. p. of 4-amino-4′-phthalimidodiphenylsulphone.

4 : 4′-Bis-o-carboxybenzamidodiphenylsulphone.—4 : 4′-Bisphthalimidodiphenylsulphone (6·5 g.) was refluxed for ½ hour with 0·5% ethyl-alcoholic potassium hydroxide (570 c.c.). The resultant clear liquid was immediately diluted with water to 3000 c.c. and cooled. Acidification with dilute hydrochloric acid gave a white precipitate, which after one recrystallisation from aqueous acetone yielded the required product (5·6 g.) (Found : C, 61·6; H, 3·9; N, 5·3; S, 5·6. $C_{28}H_{20}O_8N_2S$ requires C, 61·7; H, 3·7; N, 5·1; S, 5·9%). This on moderately rapid heating melted at 182°, frothed, and gave a solid, m. p. 300°—this was 4 : 4′-bisphthalimidodiphenylsulphone. On very slow heating, no frothing was apparent, only a slight softening at approximately 185° with final melting at 304—307°.

4 : 4′-Biscamphorimidodiphenylsulphone.—4 : 4′-Diaminodiphenylsulphone (7·5 g.), camphoric anhydride (11·0 g.; 2 mols.), and pyridine (6 c.c.) were boiled together under reflux for 14 hours. When boiled for a shorter time (1 hour), little reaction took place. The thick syrup obtained was freed from pyridine by steam-distillation and then boiled with alcohol, which caused it to crystallise (1·2 g.). The solid was purified by solution in cold chloroform and gradual addition of alcohol; m. p. 375°. It formed short columns, almost insoluble in alcohol, acetone, dioxan or water, but readily soluble in chloroform or pyridine (Found : C, 65·5; H, 6·2; N, 4·7; S, 5·2. $C_{32}H_{36}O_6N_2S,\frac{1}{2}H_2O$ requires C, 65·6; H, 6·4; N, 4·8; S, 5·5%).

Malonyl Monochloride.—It was not found possible to prepare the acid chloride by Staudinger and Ott's method (*Ber.*, 1908, **41**, 2211). The following proved to be the best method : dry malonic acid (8 g.; 1 mol.) and pure thionyl chloride (9·7 c.c.; 1·5 mols.) were heated for 3—4 hours at 45—50°. The excess of thionyl chloride was removed from the brown mass in a vacuum at room temperature. The resultant greenish-brown solid was extracted three times with cold chloroform; addition of light petroleum precipitated crystals of the acid chloride (3 g.), m. p. 62—64° (decomp.).

The authors thank Dr. T. A. Henry for his interest and advice, Mr. P. H. J. Grove for assistance in the experimental work, and Messrs. A. Bennett and H. C. Clarke for the micro-analyses.

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12. *The Exchange Reactions of 4-Nitro-1-naphthyl Methyl Ether and 4-Nitro-1-naphthyl Ethyl Ether with Sodium Ethoxide and Methoxide respectively, and the Reduction of Certain 1-Nitronaphthalene Derivatives.*

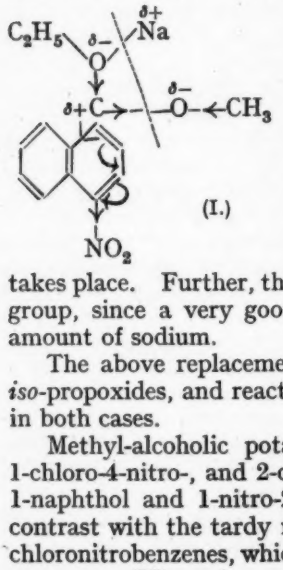
By HERBERT H. HODGSON and JOHN HABESHAW.

Nitronaphthalene derivatives are more completely reduced than the corresponding benzene compounds. Methyl-alcoholic potassium hydroxide readily replaced chlorine by the hydroxyl group in the *o*- and *p*-chloronitronaphthalenes in contrast with tardy replacement of chlorine in the *o*- and *p*-chloronitrobenzenes. 4-Nitro-1-naphthyl methyl ether reacted with sodium ethoxide in excess of ethyl alcohol to give 4-nitro-1-naphthyl ethyl ether, and 4-nitro-1-naphthyl ethyl ether reacted with sodium methoxide in excess of methyl alcohol to give 4-nitro-1-naphthyl methyl ether. These exchange reactions are discussed.

UNDER neutral conditions the nitronaphthalenes are reduced more completely than nitrobenzene (cf. Cumming and Steele, J., 1923, **123**, 246), and this greater facility of reduction is now established for 4-chloro-1-nitronaphthalene and 4-nitro-1-naphthyl methyl ether, which are reduced as far as the azo-stage. These facts indicate that the nitro-group in the nitronaphthalenes and their derivatives is more

positive than in the corresponding benzene compounds, and this can be ascribed to the additional negative (—*I*) inductive effect of the second benzene nucleus (Hodgson and Elliot, J., 1935, 1850; *J. Soc. Dyers and Col.*, 1938, **54**, 264).

Treatment of 4-nitro-1-naphthyl methyl ether with a deficiency of sodium ethoxide in ethyl alcohol for 10 minutes resulted in replacement of methoxyl by ethoxyl, the nitro-group remaining unattacked. This exchange did not take place with *p*-nitroanisole, which reacted at the nitro-group to give a mixture of *p*-azoxy- and *p*-azo-anisoles (cf. Rotarski, *Ber.*, 1903, **36**, 3158). Conversely, when sodium methoxide reacted with 4-nitro-1-naphthyl ethyl ether in methyl-alcoholic solution, a corresponding exchange of ethoxyl for methoxyl occurred. Such an easy reversal of behaviour might be tentatively explained as follows: The 1-carbon atom in 4-nitro-1-naphthyl methyl ether is very strongly kationoid owing to a combination of the (—*I*) effects of the nitro-group and the second nucleus, and the attached methoxy-group has also a negative (—*I*) inductive effect (cf. Ingold, *Ann. Reports*, 1928, **25**, 122; Hodgson and Clay, J., 1929, 2776). The net result is a very strained polarised covalent link, which in consequence is subject to attack by the strongly anionoid reagent sodium ethoxide (I) with resulting displacement of methoxyl by ethoxyl. In 4-nitro-1-naphthyl ethyl ether, exactly the same set of electronic conditions obtains as in the methyl ether, *viz.*, a strained polarised covalent linkage between the ethoxy-group and the attached 1-carbon atom, with consequent attack by the powerful anionoid reagent (sodium methoxide) whereby replacement of ethoxyl by methoxyl takes place. Further, the action of the sodium is apparently catalytic, *i.e.*, it is the carrier of the alkoxy-group, since a very good yield of exchange product is obtained with less than the stoicheiometric amount of sodium.

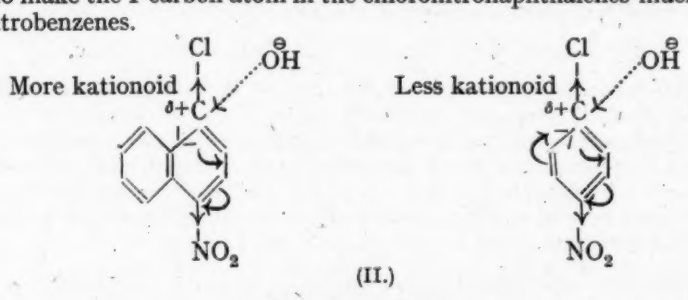


(I.)

The above replacements, however, failed to occur with the more readily oxidisable sodium *n*- and *iso*-propoxides, and reaction was probably at the nitro-group, since insoluble coloured mixtures resulted in both cases.

Methyl-alcoholic potassium hydroxide displaced chlorine readily at 55° from 1-chloro-2-nitro-, 1-chloro-4-nitro-, and 2-chloro-1-nitro-naphthalene to give the potassium salts of 2-nitro- and 4-nitro-1-naphthol and 1-nitro-2-naphthol, respectively, in *ca.* 90% yield. These reactions are in striking contrast with the tardy reactivity of either aqueous or alcoholic potassium hydroxide with 1- and 4-chloronitrobenzenes, which for complete conversion into the 1- and 4-nitrophenols require heating under pressure. When, however, sodium or potassium methoxide or ethoxide was heated with the above chloronitronaphthalenes or chloronitrobenzenes, the halogen was replaced with ease by the methoxy- or ethoxy-group. These results indicate that the dipolarised alkoxides are much more powerful anionoid reagents than the ionic alkali hydroxides.

The following tentative explanation is offered to explain the great difference between the reactivities of *o*- and *p*-chloronitronaphthalenes and *o*- and *p*-chloronitrobenzenes towards alcoholic alkali hydroxides. The hydroxyl ion (with completed octet of electrons) is very stable compared with the polarised alkoxides and will only react at a powerful kationoid centre. Now the carbon atom to which chlorine is attached in the chloronitronaphthalenes differs from that in the chloronitrobenzenes by the negative (—*I*) effect due to the second nucleus, which makes it more kationoid, and owing to the less mobile (Erlenmeyer) structure of naphthalene, relief of strain (to produce less positivity) is well-nigh impossible, whereas in the chloronitrobenzenes this accommodation is possible from the third double bond (II). Both these influences combine to make the 1-carbon atom in the chloronitronaphthalenes much more kationoid than that in the chloronitrobenzenes.



(II.)

Experimental.

Neutral Reduction of 4-*Chloro*-1-*nitronaphthalene.*—The chloronitro-compound (10 g.) in ethyl-alcoholic solution was treated with zinc dust (30 g.) according to the directions of Cumming and Steele (*loc. cit.*).

(The use of less zinc dust produced tar and not the azoxy-compound.) The somewhat tarry product was crystallised once from glacial acetic acid, by which the tar was removed, and then three times from benzene, 4 : 4′-*dichloro*-1 : 1′-*azonaphthalene* being obtained in *ca.* 10% yield in bright orange needles, m. p. 262—263° (Found : N, 8·1. $C_{20}H_{12}N_2Cl_2$ requires N, 8·0%).

The Action of Sodium Methoxide and Sodium Ethoxide on 4-*Chloro*-1-*nitronaphthalene*.—Hot solutions of 4-chloro-1-nitronaphthalene (2·5 g.) in methyl alcohol (30 c.c.) and in ethyl alcohol (30 c.c.) were separately treated under reflux with sodium (1·1 g.), added in small pieces and with continuous stirring at a temperature near the b. p. of each mixture. The liquids were heated for 10 minutes, filtered, and allowed to cool gradually. From the first solution 4-nitro-1-naphthyl methyl ether separated in pale yellow needles, m. p. 85° (lit., 85—86°) (Found : N, 7·1. Calc. : N, 6·9%), and from the second solution 4-nitro-1-naphthyl ethyl ether crystallised in yellow needles, m. p. 116—117° (see Heermann, later) (Found : N, 6·6. Calc. : N, 6·45%).

The Action of Methyl-alcoholic Potassium Hydroxide on 1-*Chloro*-2-*nitronaphthalene*.—The chloronitro-compound (10 g.) was heated at 55° with 25% methyl-alcoholic potassium hydroxide (100 c.c.). After 4 hours the dark red potassium salt of 2-nitro-1-naphthol was collected, washed with methyl alcohol (yield, 9·5 g.), and acidified. The 2-nitro-1-naphthol crystallised from 50% aqueous alcohol in yellow needles, m. p. 128°. Similarly, 1-nitro-2-naphthol was obtained from 2-chloro-1-nitronaphthalene in yellow needles, m. p. 103°. The process proved very convenient and satisfactory for the preparation of these nitronaphthols in the pure state.

Exchange Reactions in 4-*Nitronaphthyl Methyl and Ethyl Ethers*.—(*a*) A solution of 4-nitro-1-naphthyl methyl ether (13·5 g.) in ethyl alcohol (200 c.c.) was treated with sodium (8 g.), added gradually in small pieces and with vigorous stirring; the temperature rose to 65° and was maintained there for 10 minutes after addition was complete. The solution darkened considerably and, on cooling, deposited thick yellow needles (11 g.) of 4-nitro-1-naphthyl ethyl ether, which crystallised from ethyl alcohol in well-formed, light yellow needles, m. p. 116—117° (Heermann, *J. pr. Chem.*, 1891, **44**, 238, gives m. p. 116—117°) (Found : N, 6·6. Calc. : N, 6·45%).

(*b*) Solutions of 4-nitro-1-naphthyl ethyl ether (5 g.), obtained as in (*a*) and also by the action of sodium ethoxide on 1-chloro-4-nitronaphthalene, in methyl alcohol (75 c.c.) were treated under reflux as in (*a*) with sodium (3 g.); the quantities are approximately the equivalents of those in (*a*). When the solutions cooled, they deposited 4-nitro-1-naphthyl methyl ether, which crystallised from dilute ethyl alcohol in long, pale yellow needles, m. p. 85° (Found : N, 7·0. Calc. : N, 6·9%), identical with the initial material used in (*a*).

(*c*) Reactions (*a*) and (*b*) were repeated with sodium in *n*-propyl and *iso*propyl alcoholic solutions, but only coloured amorphous uncrystallisable substances resulted. In attempts to carry out the reactions at room temperature and without subsequent heating the initial materials were recovered unchanged.

Some Reductions of 4-*Nitro*-1-*naphthyl Methyl and Ethyl Ethers*.—(*a*) By the usual reduction method with zinc dust and alkali hydroxide, only small amounts of 4-amino-1-naphthyl methyl ether (identified by the acetyl derivative) and 4-amino-1-naphthyl ethyl ether (isolated by steam-distillation) were obtained, the rest of the product being insoluble tar.

(*b*) 4-Nitro-1-naphthyl methyl ether (2·5 g.), reduced according to the directions of Cumming and Steele (*loc. cit.*), afforded a tarry product, from which, after one crystallisation from glacial acetic acid and several from ethyl alcohol, 4 : 4′-*dimethoxy*-1 : 1′-*azonaphthalene* (0·5 g.) was obtained in short orange-yellow needles, m. p. 105—107° (Found : N, 8·4. $C_{22}H_{18}O_2N_2$ requires N, 8·2%). It was necessary to use a large excess of zinc dust before any definite product whatever could be isolated from the reduction mixture.

(*c*) The most favourable conditions for the reduction of 4-nitro-1-naphthyl ethyl ether to the amine were as follows : A solution of crystallised stannous chloride (5 g.) in hydrochloric acid (25 c.c., *d* 1·16) was added gradually to a boiling solution of 4-nitro-1-naphthyl ethyl ether (2 g.) in glacial acetic acid (75 c.c.), the boiling under reflux being continued for 20 minutes after the addition was complete. On cooling, 4-amino-1-naphthyl ethyl ether hydrochloride separated (1·6 g.; yield, *ca.* 80%); this crystallised from ethyl alcohol in fine colourless needles, m. p. 275° (Heermann, *J. pr. Chem.*, 1892, **45**, 545, gives m. p. 275°) (reddened at *ca.* 260° and melted to a deep red liquid) (Found : Cl, 15·6. Calc. : Cl, 15·9%). The amine was liberated from the hydrochloride by treatment with dilute aqueous ammonia, isolated by steam distillation, and crystallised from light petroleum; it formed colourless needles, m. p. 96° (Heermann, *loc. cit.*, gives m. p. 96°) (Found : N, 7·6. Calc. : N, 7·5%), which rapidly became discoloured on exposure to air.

The yields obtained by reduction with stannous chloride in alcohol were *ca.* 50%.

In the case of 4-nitro-1-naphthyl methyl ether a dilution of 90 c.c. of glacial acetic acid was required for control of the somewhat violent reaction, and 4-amino-1-naphthyl methyl ether hydrochloride did not crystallise when the reaction mixture had cooled. The solution was made nearly alkaline with sodium carbonate and finally alkaline with aqueous ammonia, and then steam-distilled. 4-Amino-1-naphthyl methyl ether passed over as an oil which did not crystallise on cooling (cf. Woroshzow, *Chem. Zentr.*, 1911, I, 650; Hodgson and Smith, J., 1935, 671); it was identified by its acetyl derivative, which crystallised from alcohol in colourless needles, m. p. 187° (Hodgson and Smith, *loc. cit.*, give m. p. 187°).

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TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, July 25th*, 1941.]

13. *The Interaction of Betaine with Primary Aromatic Amines, Organic Disulphides, and Sodium Sulphite.*

By Frederick Challenger, Philip Taylor, and (in part) Bernard Taylor.

When betaine (free from hydrochloride) is heated with primary aromatic amines, the corresponding *N*-monomethyl derivatives are formed. Much trimethylamine is also produced, but ammonia and mono- or di-methylamine appear to be absent. The arylaminoacetoarylamide R·NH·CH_2·CO·NHR is formed in most cases and isolated as the hydrochloride. Glycine ethyl betaine and aniline similarly give ethylaniline. Diphenyl, di-*n*-butyl, and di-*n*-amyl disulphides also react with betaine at their boiling points, undergoing fission to give phenyl methyl sulphide, methyl *n*-butyl sulphide, and methyl *n*-amyl sulphide respectively. These reactions are clearly related to the isomerisation of betaine by heat, giving methyl dimethylaminoacetate (Willstätter), and to the formation of dimethyl sulphide, selenide, and telluride observed when betaine is heated with sodium sulphite, selenite, or tellurite.

Willstatter (*Ber.*, 1902, **35**, 584) and Willstätter and Kahn (*ibid.*, 1904, **37**, 401, 1853) showed that at 300° a methyl group in betaine is eliminated from the nitrogen atom and transferred to the −CO·O group, giving the isomeric methyl dimethylaminoacetate in a minimal yield of 50%. Straw and Cranfield (*J. Soc. Chem. Ind.*, 1936, **55**, 40T) obtained only a 30% yield. The reaction is reversible:

$$\overset{+}{N}Me_3\cdot CH_2\cdot CO\cdot \bar{O} \rightleftarrows NMe_2\cdot CH_2\cdot CO_2Me$$

Glycine ethyl betaine similarly gives ethyl diethylaminoacetate, and the dimethylethyl and methyldiethyl betaines of glycine give the methyl esters of methylethylglycine and diethylglycine in yields of 50, 50, and 35%. In alkylmethyl betaines, therefore, only the methyl group appears to migrate.

Riesser (*Z. physiol. Chem.*, 1913, **86**, 440) suggested that a similar elimination of a methyl group from betaine or choline in the animal body might account for the formation of the garlic odour, resembling that of dimethyl telluride, which is exhaled by animals after ingestion of potassium tellurite.

It has never been proved that this odour is due to dimethyl telluride, although one of us with Bird (J., 1939, 163) and North (J., 1934, 68) has shown that cultures of *Scopulariopsis brevicaulis* and other moulds on media containing tellurite and selenite evolve dimethyl telluride and selenide respectively. For further references to the methylating action of the animal body, see Challenger and Higginbottom, *Biochem. J.*, 1935, **29**, 1760; Challenger, *J. Soc. Chem. Ind.*, 1935, **54** (*C. and I.*), 657; Bird and Challenger, *loc. cit.*

Riesser (*loc. cit.*) found support for his suggestion in the observation that a mixture of betaine hydrochloride or choline chloride with sodium formate and tellurite, when heated, evolved an odour resembling that of dimethyl telluride. Challenger and Higginbottom (*loc. cit.*), using betaine free from hydrochloride, confirmed the formation of this substance. Moreover, betaine and sodium selenite, with or without formate, gave dimethyl selenide on heating. This was also obtained by heating a mixture of sodium selenite, sodium formate and tetramethylammonium hydroxide. Stanek (*Z. Zuckerind.*, 1903, **27**, 479) states that in a sealed tube at 270—280° betaine gives trimethylamine, carbon dioxide, glycollic acid, and tetramethylammonium hydroxide.

The reaction has now been extended to sulphur, dimethyl sulphide being obtained by using sodium sulphite and betaine. In view of the relation of these, admittedly pyrogenic, reactions to theories of the mechanism of biological methylation, which will be fully discussed in a forthcoming publication (see also Riesser, *loc. cit.*; Challenger and Higginbottom, *loc. cit.*; du Vigneaud *et al.*, *J. Biol. Chem.*, 1940, **134**, 787; **135**, 223), it seemed of interest to study the purely chemical reactions somewhat more closely and to find other acceptors for the methyl group of betaine. It should be emphasised, however, that in some biological systems both methylation and demethylation probably involve formaldehyde (Hess, Eichel, and Uibrig, *Ber.*, 1917, **50**, 351; Robinson, J., 1917, **111**, 877; Guggenheim, "Die Biogenen Amine," Basel, 1940, **31**, 192).

It has now been shown that when betaine (carefully freed from hydrochloride in order to avoid formation of methyl chloride) is heated with aniline, *p*-toluidine, *p*-anisidine, *p*-phenetidine or β-naphthylamine, the corresponding monomethyl derivative is formed. Much trimethylamine is also produced, but ammonia, and mono- or di-methylamine appear to be absent. An important product of the reaction in almost every case is the arylaminoacetoarylamide R·NH·CH_2·CO·NHR, isolated as the hydrochloride. This probably arises thus: $\overset{+}{N}Me_3\cdot CH_2\cdot CO\cdot \bar{O} + 2NH_2Ph = NMe_3 + H_2O +$ NHPh·CH_2·CO·NHPh. When glycine ethyl betaine is heated with aniline, ethylaniline is produced;

the yield is much smaller than that of methylaniline in the corresponding experiment with ordinary betaine.

When boiled with betaine, diphenyl, di-*n*-butyl, and di-*n*-amyl disulphides are converted into phenyl methyl sulphide, methyl *n*-butyl sulphide, and methyl *n*-amyl sulphide respectively. This reaction is of interest in view of the fission and methylation which the two aliphatic disulphides and their lower homologues undergo in bread cultures of *S. brevicaulis* (Challenger and Rawlings, J., 1937, 868; Blackburn and Challenger, J., 1938, 1872).

Willstätter (*Ber.*, 1902, **35**, 584) points out that the conversion of betaine into the isomeric ester does not lend itself to kinetic study. Kuhn and Giral (*Ber.*, 1934, **67**, 1130; 1935, **68**, 387) conclude that the reaction is almost certainly not intramolecular, at any rate in the case of the long-chain ξ-trimethylpentadeca and π-trimethylheptadeca-betaines, which have a very high dipole moment in alcoholic solution and also undergo this isomerisation on heating. This is in agreement with modern views on several similar reactions, and is supported by our work, the mobile methyl group being intercepted by the selenite, tellurite or primary amine.

Willstätter's results and our own can be conveniently explained on the assumption that a positively charged methyl group is liberated from the betaine molecule (see, however, p. 50). In the betaine–ester conversion this attaches itself to the negative oxygen of a second molecule, which thus acquires a positive charge. This then expels a positive methyl group, which attaches itself to the negative oxygen of the first molecule:

$$\left.\begin{matrix}\overset{+}{\mathrm{N}}\mathrm{Me_3}\cdot\mathrm{CH_2}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}} \\ \bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\overset{+}{\mathrm{N}}\mathrm{Me_3}\end{matrix}\right\} \longrightarrow \left.\begin{matrix}\mathrm{NMe_2}\cdot\mathrm{CH_2}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}}\boxed{^{(+)}\mathrm{Me}} \\ \boxed{^{(+)}\mathrm{Me}}\bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\mathrm{NMe_2}\end{matrix}\right\} \longrightarrow 2\mathrm{NMe_2}\cdot\mathrm{CH_2}\cdot\mathrm{CO}\cdot\mathrm{OMe}$$

In the case of the primary amines the positive methyl ion is presumably trapped by the unshared electrons of the nitrogen atom, a proton being expelled which gives dimethylglycine with the $\mathrm{NMe_2}\cdot\mathrm{CH_2}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}}$ ion, $\mathrm{NH_2Ph} + \overset{+}{\mathrm{Me}} \longrightarrow \overset{+}{\mathrm{N}}\mathrm{H_2PhMe} \longrightarrow \mathrm{NHPhMe} + \mathrm{H^+}$.

The selenite, tellurite, and sulphite ions could similarly co-ordinate the methyl group, giving neutral $\mathrm{CH_3}\cdot\mathrm{SeO_3Na}$ (etc.), which on thermal decomposition would presumably yield dimethyl selenide, telluride, or sulphide.

In this connection it should be mentioned that, when potassium methaneselenonate $\mathrm{CH_3}\cdot\mathrm{SeO_3K}$ (Bird and Challenger, forthcoming publication) is heated, it decomposes explosively, giving a strong odour of an organic selenium compound. Potassium propane 1-selenonate gives a similar odour without exploding. The lead salts of methane- and ethane-seleninic acids also give volatile organic selenium compounds on heating. Sodium benzenesulphonate is stated by Stenhouse (*Annalen*, 1866, **140**, 287; 1869, **149**, 247) to give thiophenol, diphenyl sulphide, benzene, and thianthren on heating. On the other hand, when potassium methanesulphonate was heated in a metal-bath in a stream of nitrogen and the volatile products were absorbed in mercuric cyanide and chloride solutions, the precipitate in the cyanide was mostly mercuric sulphide, acidification giving only a faint odour of methylthiol. The mercuric chloride solution smelled slightly of dimethyl sulphide.

There would, however, appear to be sufficient evidence for the suggestion that the later stages in these betaine reactions involve the decomposition of $\mathrm{CH_3}\cdot\mathrm{SeO_3Na}$, etc.

The behaviour of the disulphides is doubtless connected with the tendency of these compounds to suffer fission with numerous reagents (see Challenger and Rawlings, *loc. cit.*, for references). The dissociation of diphenyl disulphide observed by Schönberg, Rupp, and Gumlich (*Ber.*, 1933, **66**, 1932) gave *neutral* free radicals. The reaction with betaine may be represented as the co-ordination of a positive methyl group by the disulphide, followed by expulsion of a positively charged $\overset{+}{\mathrm{S}}\mathrm{R}$ radical, thus:

$$\mathrm{R}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}:\mathrm{R} + \overset{+}{\mathrm{Me}} = \left[\mathrm{R}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}:\underset{\mathrm{Me}}{\overset{\cdot\cdot}{\mathrm{S}}}:\mathrm{R}\right]^+ = \mathrm{R}:\underset{\mathrm{Me}}{\overset{\cdot\cdot}{\mathrm{S}}}: + \left[\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}:\mathrm{R}\right]^+$$

The $\overset{+}{\mathrm{RS}}$ ion would presumably react with the $\mathrm{NMe_2}\cdot\mathrm{CH_2}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}}$ ion, but the reaction mixture has not been examined for products other than methyl sulphides, R·SMe.

As an alternative, preliminary dissociation into the ions $\bar{\mathrm{RS}}$ and $\overset{+}{\mathrm{RS}}$ may be assumed.

The reactions with sulphite, selenite, etc., may also be expressed in a somewhat different manner. The oxy-acids of sulphur, selenium and tellurium, and presumably their salts, will doubtless form

compounds with betaine analogous to the hydrochloride, *e.g.*, $\overset{+}{N}Me_3\cdot CH_2\cdot CO\cdot OH\}\overset{-}{S}eO_3H$. Potassium iodide and betaine form a compound $(C_5H_{11}O_2N)_2,KI,2H_2O$ (Willstätter, *Ber.*, 1902, **35**, 598; see also Körner and Menozzi, *Gazzetta*, 1883, **13**, 351). With primary aromatic amines, analogy would suggest that a complex such as $\overset{+}{N}Me_3\cdot CH_2\cdot CO\cdot OH\}\overset{-}{N}HAr$ might possibly be formed, but no mention of compounds of this type appears in the literature. Although aniline and betaine in molecular proportion form a hard mass, suggesting the possible formation of a compound (see p. 51), the whole of the aniline is removable on extraction with cold benzene. No such formation of solid is observed with *m*-toluidine or *p*-phenetidine.

The formation of an -onium compound from betaine and a disulphide is impossible, but a compound such as $\overset{+}{N}Me_3\cdot CH_2\cdot CO\cdot OH\}\overset{-}{S}R$ might possibly exist; the type, however, is not mentioned in Beilstein's "Handbuch." No evidence of compound formation is observed on mixing betaine and thiophenol.

The kinetics of the elimination of the alkyl group from substituted ammonium and sulphonium compounds in aqueous solution at about 100° has been studied by Ingold and his collaborators (see especially J., 1933, 526, 1571; 1935, 236, 244, 255). They have shown that the reactions $R\cdot\overset{+}{N}R'R''R'''\}\overset{-}{X} = RX + NR'R''R'''$ and $R\cdot\overset{+}{S}R'R''\}\overset{-}{X} = RX + R'R''S$ may be unimolecular or bimolecular according to the polar character of R and X. The unimolecular reaction proceeds by the separation of an ion $\overset{+}{R}$, which then unites with $\overset{-}{X}$, but in the bimolecular type of reaction no free ion is eliminated.

In the absence of any evidence as to the kinetics of the various betaine decompositions described in this communication—they occur at high temperatures—it is impossible to say whether a free methyl ion is concerned in the reactions with sulphite, selenite and tellurite, where formation of an -onium compound might be expected. In the case of those with amines and disulphides, where this appears less likely, the same doubt exists, since it would be possible for a methyl group to be transferred from betaine to the amine or disulphide by Ingold's bimolecular mechanism, followed by expulsion of $\overset{+}{H}$ or $\overset{+}{R}S$. The second of these possibilities would represent a reversal of the reaction $NH_3 + Alk\overset{+}{S}R_2 \rightleftarrows Alk\overset{+}{N}R_3 + R_2S$ envisaged by Hughes and Ingold (J., 1935, 251).

Hickinbottom (J., 1934, 1700; 1937, 1119) has suggested that a positive alkyl group may be concerned in the conversion of *N*-alkylaniline hydrogen halides into nuclear alkylated anilines by heating at 300° (Hofmann–Martius reaction). See also Watson, *Ann. Reports*, 1939, 204. The temperature of our betaine–amine experiments—about 200°—is lower than that of the Hofmann–Martius reaction, but as a check the unchanged aniline in Expt. I*a* was converted through the diazonium salt into chlorobenzene. This was pure and showed no trace of homologues on distillation.

Straw and Cranfield (*J. Soc. Chem. Ind.*, 1936, **55**, 40T) state that small quantities of formaldehyde are present in the distillate obtained on heating betaine at 280—300° in a stream of air. This conclusion was based on odour, reducing properties, and action on decolourised magenta, but the authors state that no formaldehyde could be detected by absorption of the volatile decomposition products in aqueous sodium bisulphite. Compare also Dechamps (*Bull. Soc. Chim. Belg.*, 1930, **39**, 67), who fused betaine and detected formaldehyde colorimetrically.

It seemed improbable that the methyl derivatives described in this communication, particularly those obtained from the disulphides, could be produced by traces of formaldehyde arising from the betaine. In view of the methylation of ammonium chloride by formaldehyde (Werner, J., 1917, **111**, 844) and the work of Clarke, Gillespie, and Weisshaus (*J. Amer. Chem. Soc.*, 1933, **55**, 4571) on the use of formaldehyde and formic acid in the methylation of primary amines (see also Frankland, Challenger, and Nicholls, J., 1919, **115**, 198) experiments were, however, carried out to test this possibility.

When paraformaldehyde was boiled with aniline for 10 hours, the amounts of monomethylaniline, as judged by the weights of crude *N*-nitroso-*N*-methylaniline obtained in three experiments, were less than those obtained from betaine and aniline (Expts. I and I*a*) in spite of the fact that considerable quantities of paraformaldehyde were used.

No odour of dimethyl selenide or dimethyl telluride was observed on heating sodium selenite or potassium tellurite with paraformaldehyde at 220—230° and 200—210°, respectively, or at 270°.

The work of du Vigneaud and his colleagues (*J. Biol. Chem.*, 1939, **131**, 57; 1940, **134**, 787; **135**, 223) has established the conversion of trideuteromethionine, $CD_3\cdot S\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CO_2H$, into isotopic choline in the rat, over 56% of the CD_3 group being transferred to nitrogen. This reaction is reversible (du Vigneaud, *ibid.*, 1941, **140**, 638). It therefore became of interest to determine whether the

methyl group of ordinary methionine could be transferred to aniline at its boiling point. In the single experiment which was carried out, no trace of methylaniline could be detected.

Experimental.

I. *Betaine and Aniline.*—A mixture of aniline (80 g.; 1 mol.) and betaine (104 g.; 1·03 mols.) was heated under reflux for 8·3 hours. Dilution with water, addition of aqueous sodium hydroxide, extraction with ether, and drying over sodium sulphate (a process employed in all the analogous experiments) yielded an oil (80 g.). A portion of this (35 g.) with hydrochloric acid (98 c.c.) and water (125 c.c.) gave a solid (A). [The weight was not recorded, but in another experiment aniline (6 g.) and betaine (7·5 g.) gave 0·7 g. of A.] This was separated (see below), and the filtrate cooled in ice, treated with a slight excess of sodium nitrite, and extracted with ether. The extract was washed with sodium hydroxide solution and with water and dried over sodium sulphate, giving an oil (8 g.). This oil, containing *N*-nitroso-*N*-methylaniline, was dissolved in a mixture of anhydrous ether (16 g.) and alcoholic hydrogen chloride (32 g.) and after 2 days a yellow hydrochloride was separated. Treatment with aqueous sodium hydrogen carbonate and extraction with ether yielded a green solid, which was recrystallised several times from benzene; it then formed blue prisms, m. p. 116°. The m. p. was also 116° on recrystallisation from water (green leaflets) and in admixture with authentic *p*-nitrosomethylaniline, m. p. 116° (Fischer and Hepp, *Ber.*, 1886, **19**, 2992).

The solid (A) was a hydrochloride which with aqueous sodium hydroxide gave a base (B), m. p. 111—112°, on repeated crystallisation from aqueous alcohol [Found: C, 74·4, 74·2; H, 6·4, 6·1; N, 12·35, 12·9; *M* (camphor), 231, 231. Calc. for $C_{14}H_{14}ON_2$: C, 74·3; H, 6·25; N, 12·4%; *M*, 226].

Anilinoacetanilide was prepared by boiling aniline (4 mols.) with chloroacetyl chloride (1 mol.) for 10 mins. (Meyer, *Ber.*, 1875, **8**, 1158). On repeated crystallisation from dilute alcohol it melted at 111°, alone and in admixture with the base (B). Both specimens gave white hydrochlorides. That from (B) decomposed at 205—208° after two crystallisations from alcohol, the authentic hydrochloride at 205—212°, and the mixture at 205—212° when heated fairly rapidly. The original solid (A) after two crystallisations from alcohol decomposed at 205—207°, and at 205—212° in admixture with authentic hydrochloride.

Anilinoacetanilide hydrochloride is stated by Motylewski (*Bull. Int. Acad. Pol.*, 1926, *A*, 93) to melt at 216°.

Anilinoacetanilide (B) with sodium nitrite and dilute hydrochloric acid in ice-cold alcohol gave a solid which separated from aqueous alcohol in pale yellow crystals, m. p. 142—143° (decomp.) alone and in admixture with *N*-nitrosoanilinoacetanilide, m. p. 142—143°, prepared from the authentic base in the same manner (Motylewski, *loc. cit.*, gives m. p. 145°) [Found for the specimen from base (B): C, 66·0; H, 5·35; N, 16·6. Found for the authentic specimen: C, 66·1; H, 5·3; N, 16·7. Calc. for $C_{14}H_{13}O_2N_3$: C, 65·9; H, 5·1; N, 16·5%].

In a second experiment in which aniline (13·4 g.; 1 mol.) and betaine (16·8 g.; 1 mol.) were heated for 12 hours the evaporated ethereal extract of the basified product (15 g.) was treated with aqueous zinc chloride (16·5 g. in 37·5 c.c. of water) to remove most of the aniline (see Frankland, Challenger, and Nicholls, *loc. cit.*), and the residual bases extracted with hot light petroleum, yielding 2·9 g. of oil. This oil (1 g.) was mixed with acetic anhydride (1 g.), poured into an equal volume of water, and treated with concentrated aqueous ammonia, giving a white solid (0·8 g.), m. p. 80—90°. After three recrystallisations from light petroleum this melted at 99—100°, alone and in admixture with authentic acetomethylanilide, m. p. 99—100°.

The evolution of trimethylamine during the heating of betaine and aniline was established in two separate experiments by passing the evolved vapours through dilute hydrochloric acid. Evaporation left a deliquescent residue, soluble in chloroform and in alcohol. It was analysed without recrystallisation (Found: Cl, 37·6, 37·5, and 37·2, 37·25. Calc. for C_3H_9N,HCl: Cl, 37·1%).

I*a*. In another experiment using betaine (21 g.) and aniline (16 c.c.) it was noticed that the mixture set to a hard mass in about 2 mins., suggesting the possible formation of a compound. No rise in temperature was observed. The mixture was then heated in a paraffin bath at 205° for 9—10 hours. The bases were liberated as usual (19 g.). With hydrochloric acid (53 c.c.) and water (68 c.c.) the hydrochloride of anilinoacetanilide (3·28 g.) separated overnight. This gave no oil with sodium hydroxide and was free from the hydrochloride of aniline or methylaniline. The cooled filtrate was treated with sodium nitrite (6·0 g.) in water (15 c.c.), the *N*-nitroso-*N*-methylaniline (5 g.) extracted with ether, and the cold aqueous solution slowly added to cuprous chloride (16 g.) in hydrochloric acid (150 c.c.). The chlorobenzene so produced (2·75 g.) distilled constantly at 130°.

II. *Betaine and* p-*Toluidine.*—A mixture of betaine (2 g.; 0·91 mol.) and the amine (2 g.; 1 mol.) was heated for 8 hours; the product was cooled, treated with aqueous sodium hydroxide, and extracted with ether, yielding 2·5 g. of oil. With hydrochloric acid (5 c.c.) and water (5 c.c.) the oil gave a solid (C) (0·3 g.). This was the hydrochloride of a base which was liberated by trituration with aqueous sodium hydroxide. When recrystallised from aqueous alcohol and then from benzene, it melted at 132—133° alone, and at 133—134° in admixture with authentic *p*-toluidinoaceto-*p*-toluidide, m. p. 133—134° (Meyer, *Ber.*, 1875, **8**, 1161, gives m. p. 136°). This base gave, with sodium nitrite and hydrochloric acid in ice-cold alcohol, a solid (D),

which when recrystallised from aqueous alcohol and then from benzene had m. p. 156—159° (decomp.). In admixture with authentic *N*-nitroso-*p*-toluidinoaceto-*p*-toluidide (see p. 54), m. p. 156—159° (decomp.), another sample of (D) melted at 157—159° (decomp.) [Found for this sample of (D): C, 68·15, 68·0; H, 6·2, 6·1; N, 14·55, 14·6. $C_{16}H_{17}O_2N_3$ requires C, 67·8; H, 6·05; N, 14·85%].

With tin and hydrochloric acid, (D) gave a white solid containing no nitroso-group. On recrystallisation from methyl alcohol it melted at 134—135° and was probably *p*-toluidinoaceto-*p*-toluidide (the m. p. varied with the rate of heating).

In a further experiment betaine (6 g.; 1·03 mols.) and *p*-toluidine (5·3 g.; 1 mol.) were heated for 8 hours, and the product (4 g.) treated with hydrochloric acid (8 c.c.) and water (8 c.c.). Removal of the insoluble hydrochloride (C) and treatment of the filtrate with sodium nitrite (3 g.), extraction with ether, and washing of the extract with aqueous sodium hydroxide gave a solid, which on repeated crystallisation from light petroleum (b. p. 40—60°) gave crystals (E), m. p. 49° [Found for a sample of (E) obtained in an earlier experiment: C, 63·9; H, 7·0; N, 18·5. Calc. for $C_8H_{10}ON_2$: C, 63·95; H, 6·7; N, 18·7%]. In admixture with authentic *N*-nitroso-*N*-methyl-*p*-toluidine of m. p. 49° (Ullmann, *Annalen*, 1903, **327**, 108, gives m. p. 53°) this sample of (E) melted at 48—49°.

In the earliest experiments in which betaine and *p*-toluidine were heated together a hydrochloride other than (C) was precipitated on addition of dilute hydrochloric acid to the product of the reaction obtained as before. This hydrochloride (X) on trituration with sodium hydroxide solution gave the free *base*, m. p. 141—142°, and 143—144° after repeated crystallisation from aqueous alcohol [Found: C, 70·3, 70·45; H, 6·95, 7·0; N, 12·8, 12·95; *M* (camphor), 338. $C_{19}H_{23}O_2N_3$ requires C, 70·1; H, 7·15; N, 12·9%; *M*, 325]. The structure $(CH_3{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_2)_2N{\cdot}CH_3$ is in agreement with this molecular formula.

The reason for the formation of this compound in some experiments and not in others has not been decided. It was accompanied by some *p*-toluidinoaceto-*p*-toluidide, which was isolated as the nitroso-compound (D) along with (E), since in some experiments the hydrochlorides (C) and (X) were not removed before nitrosation.

III. *Betaine and* p-*Anisidine*.—The amine (7·6 g.; 1 mol.) and betaine (7·25 g.; 1 mol.) were boiled for 8 hours, and the product (8·5 g.) separated as before. With dilute hydrochloric acid (1 : 1; 30 c.c.) it gave a solid (F), which was separated [when *p*-anisidine (3 g.; 1 mol.) and betaine (2 g.; 0·7 mol.) were used, 0·4 g. of (F) was obtained].

The filtrate with sodium nitrite (7 g.) gave after the usual treatment a red solid (1·7 g.), which after two crystallisations from light petroleum formed yellow crystals, m. p. 44—45°, alone and in admixture with authentic *N*-nitroso-*N*-methyl-*p*-anisidine of the same m. p., prepared by the method of Hodgson and Crook (J., 1932, 1814) (Found: C, 58·1; H, 6·1; N, 16·9. Calc. for $C_8H_{10}O_2N_2$: C, 57·8; H, 6·1; N, 16·9%). (F) was a hydrochloride; the base, recrystallised from benzene and then from absolute alcohol, was white and had m. p. and mixed m. p. 131—132° with authentic *p*-anisidinoaceto-*p*-anisidide, m. p. 131—132° (see p. 54). A portion of the base was suspended in acetone, cooled in ice and salt, and treated with hydrochloric acid and sodium nitrite. The precipitate, after recrystallisation from benzene, decomposed at 153—156° when heated rapidly, giving a red liquid, and at 155—159° in admixture with authentic *N*-nitroso-*p*-anisidinoaceto-*p*-anisidide, m. p. 155—159° (decomp.).

IV. *Betaine and* p-*Phenetidine*.—The amine (8 g.; 1 mol.) and betaine (6·8 g.; 1 mol.) were boiled for 8 hours. The product (10·7 g.), isolated in the usual way, was treated with hydrochloric acid (15 c.c.) and water (30 c.c.), giving a solid (G). The filtrate with sodium nitrite (6 g.) in water (30 c.c.) gave on extraction with ether a red oil (3·3 g.) which soon solidified. Light petroleum removed a solid, which when crystallised twice from the same solvent formed pale yellow needles, m. p. 46·5—47·5°, alone and in admixture with authentic *N*-nitroso-*N*-methyl-*p*-phenetidine of the same m. p. prepared by Stedman's method (J., 1924, **125**, 1375).

The base from (G) after crystallisation from benzene and then from aqueous alcohol melted at 137—138° and at 136—137° in admixture with authentic *p*-phenetidinoaceto-*p*-phenetidide, m. p. 137—138° (see p. 54).

V. *Betaine and* β-*Naphthylamine*.—The base (9 g.; 1 mol.) and betaine (7·5 g.; 1·02 mols.) were heated for 8 hours at 200—220°. The product (7 g.) with hydrochloric acid (1 : 1, 30 c.c.) gave a solid (H). It appeared to be a hydrochloride but was not identified. Nitrosation of the filtrate gave a red oil, which after the usual treatment solidified, and after four crystallisations from alcohol formed pale yellow needles, m. p. and mixed m. p. 87—88° with authentic *N*-nitroso-*N*-methyl-β-naphthylamine, m. p. 87—88° (von Pechmann, *Ber.*, 1895, **28**, 2370) (Found: C, 70·55; H, 5·65; N, 14·75. Calc. for $C_{11}H_{10}ON_2$: C, 70·95; H, 5·4; N, 15·05%).

VI. *Betaine and Diphenyl Disulphide*.—The disulphide (8·2 g.; 1 mol.) and betaine (9 g.; 2·02 mols.) were boiled under reflux for 8 hours. The brown liquid was warmed with water and extracted with ether, and the extract washed with dilute hydrochloric acid, dried, and evaporated. The dark liquid residue (10 g.) was distilled at 23 mm. and the fraction of b. p. 100° was heated for 1 hour at 100° with excess of 3% potassium permanganate solution. After decoloration with sodium formate the mixture was extracted with ether, and the extract dried over calcium chloride and evaporated, leaving a semi-solid residue. The white solid was separated and recrystallised several times from water; it then melted at 86—87°, alone and in admixture with authentic phenylmethylsulphone of the same m. p.

A second experiment yielded fractions of b. p. 60—80° and 80—100° (20 mm.). Oxidation as before gave the sulphone of m. p. 85—86° and 87—88°.

VII. *Betaine and Di-n-butyl Disulphide.*—The disulphide (5 g.; 1 mol.), free from *n*-butylthiol and hydrogen sulphide, was boiled with betaine (6·3 g.; 1·92 mols.) for 11 hours, during which time a further 10 g. of the disulphide were added. The product, freed from betaine and bases, as in VI, formed a red oil (12·3 g.), which was distilled at the ordinary pressure. The fraction, b. p. 37—180°, (1·1 g.) was shaken mechanically with saturated aqueous mercuric chloride (500 c.c.) for 1 hour, giving a red precipitate (3·1 g.) which gradually became brown (the formation of red mercuric chloride derivatives under similar conditions is described by Challenger and Rawlings, J., 1937, 873). This was treated with sodium hydroxide solution and warmed on the steam-bath from time to time and volatile products were aspirated through one bottle of 4% aqueous mercuric cyanide and three bottles of 4% aqueous mercuric chloride (see Blackburn and Challenger, *loc. cit.*). No precipitate formed in the mercuric cyanide at any time, but a white deposit formed in the first mercuric chloride bottle after 15—30 mins. and after 8 days 0·9 g. was obtained, m. p. 105—116°. It was recrystallised twice from benzene and after slight shrinkage at 115° had m. p. and mixed m. p. 116—118° with authentic methyl *n*-butyl sulphide dimercurichloride, m. p. 116—118° (Blackburn and Challenger, *loc. cit.*, p. 1875).

VIII. *Betaine and Di-n-amyl Disulphide.*—The disulphide (4 g.; 1 mol.) and betaine (3 g.; 1·32 mols.) were boiled for 8 hours. The product (4·3 g.), obtained as in VII, was distilled at the ordinary pressure, giving 1·5 g. of a yellow oil, b. p. above 60°; 1 g. with saturated aqueous mercuric chloride (300 c.c.) gave a pink solid (3·1 g.). Aspiration of this in alkaline suspension as in VII gave no precipitate in the mercuric cyanide during 21 days, but in 24 hours 0·16 g. of solid, m. p. 123—127°, formed in the first mercuric chloride bottle. After four crystallisations from benzene this had m. p. and mixed m. p. 125—126° with authentic methyl *n*-amyl sulphide mercurichloride of the same m. p. (Blackburn and Challenger, *loc. cit.*, p. 1875). During the next 20 days a further deposit (0·6 g.), m. p. 124—126°, formed in the mercuric chloride.

The remainder of the crude distillate (0·5 g.) was treated with 2·5 c.c. of perhydrol (30% H_2O_2) in glacial acetic acid (0·5 c.c.), heated at 100° for 1 hour under reflux, cooled, and extracted with chloroform. The extract, washed with sodium bicarbonate solution and dried over calcium chloride, yielded an oil which solidified in ice and salt. After three crystallisations from ether–light petroleum it had m. p. and mixed m. p. 35—36° with authentic methyl-*n*-amylsulphone of the same m. p. (see p. 54).

Diethylaminoacetic Acid Ethyl Betaine.—" Triethyl betaine " was prepared by a modification of Hofmann's method (*Proc. Roy. Soc.*, 1862, **11**, 526) from triethylamine (32 g.; 1·2 mols.) and ethyl chloroacetate (33 g.; 1 mol.) by heating with absolute alcohol (40 c.c.) under reflux for 24 hours. A sealed tube is not necessary. The quaternary salt was precipitated with dry ether, giving an oil which solidified overnight. This was separated (yield, about 53 g.) and dissolved in water, adhering ethyl chloroacetate removed by three extractions with ether, and the aqueous solution evaporated twice at 100° to remove triethylamine. The aqueous solution was then shaken for 2½ hours with silver oxide (1·3 mols.) prepared from silver nitrate (57 g.) and potassium hydroxide (19 g.), filtered, and evaporated under diminished pressure, then in an open vessel at 100°, and the residue dried in a desiccator; yield, 24 g. of a brownish solid. This was dried for 56 hours at 105°. Another specimen gave with aqueous picric acid a picrate, m. p. 196—198° after two recrystallisations from water. Ingold and Rothstein (J., 1931, 1682), who prepared it from ethyl diethylaminoacetate and ethyl iodide, give m. p. 193—194°.

IX. *Diethylaminoacetic Acid Ethyl Betaine and Aniline.*—The betaine (20 g.; dried at 105°) and aniline (12 g.) were boiled for 10 hours, and the product made alkaline with sodium hydroxide and extracted with ether, yielding 19 g. of oil. This was well stirred with a solution of zinc chloride (21 g.) in water (50 c.c.), giving a viscid solid. After filtration this was well washed with light petroleum and with ether and then extracted under reflux for 4 hours with boiling light petroleum. The dried solvents were evaporated, giving 0·9 g. of an oil having an odour of ethylaniline. Treatment with acetic anhydride (0·9 g.), dilution with water, addition of a slight excess of ammonia (compare Morgan and Grist, J., 1918, **113**, 691), and leaving below 0° gave an oil. A portion of this solidified on nucleation with ethylacetanilide and a trace of the resulting solid was used to nucleate the remainder of the oil, giving a white solid (0·4 g.), m. p. 47—53°. After successive crystallisations from ethyl acetate, ether and ethyl acetate this melted at 51—53° alone and in admixture with authentic ethylacetanilide, m. p. 51—53°.

X. *Methionine and Aniline.*—Methionine (2·3 g.; 1 mol.) and aniline (8·2 g.; 5·7 mols.) were heated in an oil-bath at 190—210° for 10·5 hours. Traces of ammonia and a mercaptan were evolved but the methionine appeared unchanged. Basification, extraction with ether, evaporation of the solvent, distillation in steam, and extraction with ether finally yielded 5·7 g. of almost pure aniline, b. p. 183—185°. No oily drops of nitrosoamine were produced on diazotisation of this or of the slight residue in the distillation flask. The characteristic odour of methylaniline was absent throughout the experiment.

XI. *Aniline and Paraformaldehyde.*—(*a*) Aniline (18·6 g.; 1 mol.) and paraformaldehyde (trioxymethylene, 12·0 g.; 2 mols.) were heated on a sand-bath. Water was eliminated at about 130°. The mixture was then gradually heated in an oil-bath, under reflux; a vigorous reaction occurred at 210°, giving a dark red tar. Distillation in steam gave only 1—2 c.c. of oil still containing aniline. This was dissolved by addition of hydrochloric acid, and sodium nitrite added. Extraction with ether yielded only 0·7 g. of a dark oil containing

a little *N*-nitroso-*N*-methylaniline. This result may be compared with that of Expt. I*a*, where 5 g. of a much purer nitrosoamine were obtained by the use of betaine.

(*b*) Aniline (186 g.; 10 mols.) and paraformaldehyde (12 g.; 2 mols.) were heated in an oil-bath. A clear solution was obtained at 120° and water separated at 140°. The temperature was raised to 210°, where it was maintained for 11 hours. No violent reaction occurred at any time. The product was dissolved in dilute hydrochloric acid (475 c.c. of concentrated acid and 150 c.c. of water) and diazotised. Much red resin was produced, but extraction with benzene and ether removed very little of this. Evaporation of the extract after washing with aqueous sodium bicarbonate and with water, and drying over sodium sulphate yielded 4·5 g. of the nitrosoamine almost free from phenol. Reduction with tin and hydrochloric acid, basification, and distillation in steam yielded 1·5 g. of methylaniline, b. p. 190—195°. This was characterised by heating at 100° with 2 : 4-dinitrochlorobenzene, *N*-methyl-2 : 4-dinitrodiphenylamine, m. p. 165—167°, being obtained. Reitzenstein (*J. pr. Chem.*, 1903, **68**, 255) gives m. p. 167°.

(*c*) Repetition of Expt. XI (*b*) gave 2·7 g. of crude nitrosoamine.

XII. *Betaine and Sodium Sulphite.*—Betaine (5 g.) and anhydrous sodium sulphite (5 g.) were heated on a sand-bath in a stream of carbon dioxide, which then passed through (*a*) dilute hydrochloric acid (1 : 1; three bottles) to remove trimethylamine, (*b*) saturated aqueous mercuric cyanide (3 bottles), (*c*) an aqueous suspension of mercuric iodide, and finally (*d*) two bottles containing aqueous mercuric chloride. The greenish-yellow solid which separated in (*b*) was presumably a compound of mercuric sulphide and mercury dimethylthiol (Challenger and Rawlings, J., 1937, 873). No alteration occurred in (*c*), but a white solid (0·4 g.) separated in (*d*). This with sodium hydroxide gave an odour of an alkyl sulphide. Extraction with hot benzene yielded white crystals, m. p. and mixed m. p. 155—160° with authentic dimethyl sulphide mercurichloride, m. p. 155—160°. All the specimens showed shrinkage from 150—155°. Mercurichlorides of this type tend to lose alkyl sulphide below their m. p.

The yield from two experiments was treated with sodium hydroxide under ether, and the extract left with aqueous potassium platinochloride overnight. Evaporation of the ether left a residue, which was crystallised twice from hot water; it formed pale yellow needles, m. p. and mixed m. p. 160°, with authentic bis(dimethyl sulphide)platinous chloride, $2(CH_3)_2S{\cdot}PtCl_2$. Enebuske (*J. pr. Chem.*, 1888, **38**, 358) gives m. p. 159°.

Preparation and Reactions of Reference Compounds.—N-*Nitroso*-p-*toluidinoaceto*-p-*toluidide*. *p*-Toluidinoaceto-*p*-toluidide was prepared from chloroacetic acid and 3 mols. of *p*-toluidine by Meyer's method (*Ber.*, 1875, **8**, 1161). With nitrous acid in ice-cold alcohol it gave a yellow solid, which after four crystallisations from benzene melted at 156—159° (decomp.) (Found: C, 67·75, 68·0; H, 5·9, 6·05; N, 14·7, 14·75. $C_{16}H_{17}O_2N_3$ requires C, 67·8; H, 6·05; N, 14·85%).

When 0·5 g. was heated at 100° with tin (2 g.) and hydrochloric acid (14 c.c.) for 80 mins., the yellow colour disappeared. Addition of excess of sodium hydroxide and extraction with ether yielded *p*-toluidinoaceto-*p*-toluidide. When the heating was continued for 92 hours, *p*-toluidine was obtained (m. p. and mixed m. p. of the free base and the acetyl derivative).

p-Anisidinoaceto-*p*-anisidide was prepared by Meyer's method—a new method of preparation in the case of this compound. Successive crystallisation from alcohol, benzene, and alcohol gave a product, m. p. 131—132° [Found: C, 67·25; H, 6·35; N, 9·85; *M* (camphor), 263. Calc. for $C_{16}H_{18}O_3N_2$: C, 67·1; H, 6·35; N, 9·8%; *M*, 286].

N-*Nitroso*-p-*anisidinoaceto*-p-*anisidide* was prepared from the parent anisidide in acetone solution, sodium nitrite and hydrochloric acid below 0° being used. Complete solution occurred, but a solid slowly separated which was recrystallised first from benzene and then from aqueous alcohol. It melted and decomposed at 155—159° when heated rapidly (Found: C, 60·65; H, 5·7; N, 13·15. $C_{16}H_{17}O_4N_3$ requires C, 60·9; H, 5·45; N, 13·35%).

p-Phenetidinoaceto-*p*-phenetidide was obtained by Meyer's method. Alternate crystallisations from aqueous alcohol and benzene gave a product, m. p. 137—138° (Found: C, 68·9; H, 7·05. Calc. for $C_{18}H_{22}O_3N_2$: C, 68·75; H, 7·05%).

Methyl-n-*butylsulphone*. Methyl *n*-butyl sulphide (1·4 g.) in glacial acetic acid (1·4 c.c.) was heated under reflux with perhydrol (7 c.c.) for 1 hour at 100°. A vigorous reaction occurred. Extraction of the mixture with chloroform, washing the extract with sodium bicarbonate solution and water, and drying over calcium chloride gave an oil (1 g.), which solidified in ice and salt, m. p. 28—31°. After one crystallisation from cooled benzene–light petroleum and four from ether–light petroleum this melted constantly at 29—30° (Found: C, 43·5; H, 8·7. $C_5H_{12}O_2S$ requires C, 44·1; H, 8·9%).

Methyl-n-*amylsulphone*. The sulphide (1 g.) in glacial acetic acid (1 c.c.) and perhydrol (5 c.c.) were treated as for the *n*-butyl derivative. Evaporation of the chloroform extract gave an oil (0·6 g.) solidifying below 0° and melting at 31—35°. Several crystallisations from ether–light petroleum gave a white solid of constant m. p. 35—36° (Found: C, 47·05; H, 9·15. $C_6H_{14}O_2S$ requires C, 47·95; H, 9·4%).

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(Addendum, January 8th, 1942.) It has now been shown by du Vigneaud *et al.* (*J. Biol. Chem.*, 1941, **141**, 625) that on administration of trideuteromethionine to rats the methyl groups of the choline isolated from the tissues contain 72·4 atoms % of deuterium. Similar figures (73·0 and 72·4) were obtained for the methyl group of the tissue creatine and the urinary creatinine.

The authors therefore regard these reactions as true transmethylations (transfer of a methyl group as such) which do not involve the elimination of dideuteroformaldehyde, CD_2O. With an amino-group, as in ethanolamine, this would give $\cdot NH\cdot CD_2\cdot OH \longrightarrow \cdot NH\cdot CD_2H$ instead of $\cdot NH\cdot CD_3$ and the atom percentage of deuterium in the methyl group could not rise above 66·6.

Furthermore, the work of du Vigneaud (*ibid.*, 1940, **135**, 223) on the comparative action of choline and betaine in effecting the replacement of methionine by homocystine in the diet of rats, and of Stettin (*ibid.*, 1941, **140**, 143), who administered isotopic (^{15}N) betaine to rats, has furnished evidence of the demethylation of betaine with (in the last-named research) formation of isotopic glycine.

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14. *Constitution of the Starch synthesised* in vitro *by the Agency of Potato Phosphorylase.*

By W. N. Haworth, R. L. Heath, and S. Peat.

The constitution of the granular form of the starch synthesised *in vitro* by Hanes has been investigated. The methylated derivative of the polysaccharide yields on hydrolysis 2 : 3 : 6-trimethyl glucose and tetramethyl glucose and the proportion of the latter (1·5%) corresponds to a minimum chain-length of 80—90 glucose units.

It is concluded that the polysaccharide is a starch in that it is composed solely of glucose residues which are mutually united by 1 : 4-α-glucosidic linkages. The average length of its basal or unit chain, measured by the number of glucose residues, is, however, three to four times that which is found for potato or cereal starches. It is suggested that this polysaccharide, representing 85% of the total synthetic product prepared outside the intact cell by the action of a phosphorylase on glucose 1-phosphate, is related to amyloamylose. The constitution of the remaining 15% of the synthetic polysaccharide has not yet been determined.

The remarkable synthesis of a starch by the action of plant phosphorylase on glucose 1-phosphate has been described by Hanes (*Proc. Roy. Soc.*, 1940, *B*, **128**, 421; **129**, 174). In many respects the synthetic product is indistinguishable from natural starch, although some points of difference are observable. For instance, Hanes emphasises the sparing solubility of the synthetic product in hot water and the rapidity with which it retrogrades from solution. Secondly, the colour given with iodine is more brilliantly blue than the colour given by natural starch. The third, and most characteristic difference, lies in the behaviour towards β-amylase. In the case of natural starches, degradation by β-amylase ceases when some 60% of the starch substance has been converted into maltose. Synthetic starch, on the other hand, is completely converted into maltose by β-amylase and in this respect resembles the amyloamylose of Samec.

Interest obviously attaches to the further examination of the relationship between natural starch and synthetic starch and it has been possible for us, by the courtesy of Dr. Hanes, to investigate the chemical constitution and the chain-length of the synthetic starch.

During the digestion of glucose 1-phosphate with phosphorylase, the synthetic starch is deposited from solution in grains. A sample (45 g.) of this granular form was supplied to us by Dr. Hanes. It must be emphasised, however, that the granular form represents only 85% of the total starch synthesised; the remainder is not deposited but remains in solution and may be obtained therefrom by appropriate treatment. This investigation is not concerned with the soluble form of synthetic starch, which may very well exhibit a difference in chain-length from the grain form.

It was found that the behaviour of the synthetic starch towards methylating agents was entirely analogous to that of natural potato starch. By repeated treatment of the granular synthetic starch with methyl sulphate and aqueous alkali it was possible to prepare a methylated starch which contained, after purification, 44·5% of methoxyl. The methylated starch was a white powder, very sparingly soluble in cold water and insoluble in hot. It showed $[\alpha]_D^{20°}$ + 203° in chloroform solution and in this respect is not significantly different from methylated potato starch ($[\alpha]_D$ + 208°; Haworth, Hirst, and Webb, J., 1928, 2689), methylated amylose ($[\alpha]_D$ + 207°) or methylated amylopectin ($[\alpha]_D$ + 207°; Hirst, Plant, and Wilkinson, J., 1932, 2380). Hanes (*loc. cit.*) has already reported that the synthetic starch shows rotations in water and in aqueous alkali which are almost identical with those shown by potato starch.

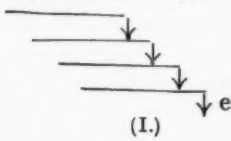
The methylated starch was separated into fractions by its precipitation from chloroform solution with light petroleum. The properties of these fractions indicated the homogeneity of the polysaccharide in a chemical sense. The viscosities of the fractions in *m*-cresol solution showed, however, variations indicating the lack of uniformity of molecular size which is a common feature of high polymers.

The modified constant $k_m = 1{\cdot}6 \times 10^{-4}$ for the Staudinger equation was suggested by Carter and Record (J., 1939, 670) to conform with osmotic pressure values determined for natural starch and with the laminated or branched structure based upon the unit chain length of 24—30 glucose residues. A synthetic starch having a unit chain-length of 100 or more glucose residues would require a different constant. If the original constant used in the Staudinger equation for cellulose chains be applied in this case, namely, $k_m = 10 \times 10^{-4}$, then the average molecular size of methylated synthetic starch, calculated from viscosity values, is 80—160 glucose residues; but this can only be a very speculative approximation, although it is not in disagreement with the value determined by the end-group method. Furthermore, Hanes (private communication) has observed that synthetic starch has a copper-reducing value consistent with its existence as a chain molecule of 100 glucose residues.

The chief product of hydrolysis of the methylated synthetic starch was 2 : 3 : 6-trimethyl glucose, some 40% of which was isolated as the crystalline 2 : 3 : 6-trimethyl β-methylglucoside. The end-group was identified in the hydrolysate by the isolation of tetramethyl methylglucoside, which was characterised as the crystalline tetramethyl glucopyranose. The quantitative estimate of the unit chain-length was made on the basis of the refractive indices and specific rotations of the fractions obtained by the distillation of the glucoside mixture from methylated synthetic starch. The proportion of tetramethyl methylglucoside found was 1·5% and this is a maximum value. The actual proportion of end-group may be less than 1·5%, but it cannot be more. The conclusion is reached that the unit chain-length of synthetic starch cannot be less than 80—90 glucose residues. From these facts it is evident that the synthetic starch is constituted on the same structural plan as natural starch, namely, that it is composed of chains of glucose residues mutually united by 1 : 4-α-glucosidic linkages. The difference between natural and synthetic starch is manifested in the number of glucose residues composing the unit chain-length.

As a first approximation, the laminated structure represented by (I) has been postulated for natural starch and other chain polysaccharides.

In the diagram (I), the horizontal lines represent the unit chain of monosaccharide residues (24—30 glucose residues in the case of natural starch) and the arrow heads indicate the linking of the reducing terminal units of the chains (cf. Haworth, Hirst, and Oliver, J., 1934, 1917; Haworth, Hirst, and Isherwood, J., 1937, 577; Haworth, *Chem. and Ind.*, 1939, **58**, 917). The union of the repeating units [represented in (I) by the points of contact of the arrow heads] has been shown (Bawn, Hirst, and Young, *Trans. Faraday Soc.*, 1940, **36**, 880) to be effected by primary valencies and recently Barker, Hirst, and Young (*Nature*, 1941, **147**, 296) have adduced evidence to show that this glycosidic union involves the primary alcohol groups at C_6 of one of the glucose residues, as was first portrayed in the formulation originally given in 1937 by Haworth, Hirst, and Isherwood (*loc. cit.*). It seems necessary to emphasise this structural formulation inasmuch as some workers in this field have erroneously assumed that the unit chain-length we have postulated is also identical with the molecular size of starch; whereas these are repeating structural units composing the much larger molecule.



(I.)

The reason for the difference in unit chain-length of natural and synthetic starch is of great interest. The suggestion might be made that the organised enzyme complex in the plant cell first assembles glucose residues in chains of 24—30 units and then completes the mutual linkage of these chains. When the enzyme system is disorganised by extraction and is functioning outside the directive influence of the intact cell, it would appear that the union of glucose residues is not limited to the formation of basal units of 24—30 residues.

It may be of course that the difference in activity of the enzyme in the starch cell and outside it is one of degree only and that basal chains much longer than are represented by 24—30 glucose units are synthesised *in vivo*. It is recognised that the unit length of chain determined by end-group assay is for the whole natural starch and that a very limited portion may well have longer chains. It is well known that starch may be separated into two constituents (amylose and amylopectin) which have widely different physical properties, but the structural difference between these constituents is by no means clear. Some vagueness attaches to the definition of the terms " amylose " and " amylopectin " and the properties of the constituents of starch appear to depend very much on the method used for their separation.

There is apparently a close similarity between the synthetic starch we have examined and the amylo-

amylose fraction of natural starch separated by the method of Samec, which involves the dispersion of potato starch in water by autoclaving at 120° and the submission of the solution to electro-dialysis. This amyloamylose is reported to be completely hydrolysed by β-amylase (Samec and Waldschmidt-Leitz, *Z. physiol. Chem.*, 1931, **203**, 16; Freeman and Hopkins, *Biochem. J.*, 1936, **30**, 446). More recently it has been reported that an amylose (about 5%) extracted with water at 60—70° from the intact grain of maize or potato starch also resembles Hanes's synthetic starch in being completely degraded to maltose by β-amylose (Meyer *et al.*, *Helv. Chim. Acta*, 1940, **23**, 865; 1941, **24**, 378). The latter workers have attempted a very rough end-group estimation of an incompletely methylated amylose from potato starch and we have used their approximate figures in a calculation of the unit length, which appears to be of the order of 300 glucose residues. The molecular weight determined by osmotic pressure measurement is of the same order.

Since this work was completed a publication has appeared by Hassid and McCready (*J. Amer. Chem. Soc.*, 1941, **63**, 2171), who have been unable to detect the presence of tetramethyl glucose in their hydrolysed specimen of methylated synthetic starch. It would appear that the quantity of the methylated polysaccharide employed for the determination (5 g.) may have been insufficient to ensure the assay of the exiguous amount (1·5%) of end-group which we, using 32 g. of initial material, have estimated.

Experimental.

The sample of synthetic starch provided by Dr. C. S. Hanes weighed 45·1 g. and contained moisture, 6·7%, and total nitrogen, 0·03%.

Methylation.—The starch was methylated in three batches.

Batch I (10 g.), dissolved in 1% sodium hydroxide solution, was treated at 50° with methyl sulphate (180 c.c.) and 30% sodium hydroxide solution (450 c.c.), added simultaneously. After the addition of one-half of the reagents, methylated starch began to separate and in order to maintain it in solution, dioxan was added. At the end of the methylation the mixture was heated on a water-bath for ½ hour and the insoluble methylated product was collected on a cloth filter. In subsequent methylations, the solvent (dioxan or acetone) was added at the beginning of the methylation. After 15 methylations, the product showed OMe, 43·8%.

Batch II (17 g.) was methylated in a similar manner except that the solvent used throughout was acetone instead of dioxan. After 12 methylations the methoxyl content was 43·5%.

Batch III (18 g.) yielded, after 12 methylations, a product containing OMe, 43·8%.

Fractional Precipitation of the Methylated Starch.—The three batches of methylated starch were now combined and dissolved in chloroform (750 c.c.). The solution was dried with anhydrous magnesium sulphate, filtered, and evaporated to small bulk. The graduated addition of light petroleum to the chloroform solution effected precipitation in fractions, the properties of which are tabulated:

Fraction.	Weight, g.	Ash, %.	OMe, % (corr. for ash).	$[\alpha]_D^{20°}$ in $CHCl_3$.	$\eta_{sp.}/c$ in *m*-cresol (c, 0·4%).	Apparent mol. wt. ($k_m = 1 \times 10^{-3}$).
A	2	34·0	—	—	—	—
B	6	1·0	42·5	+190°	0·912	18,200
C	6	0·8	44·6	+203	0·840	16,800
D	7	0·2	44·9	+203	1·537	30,700
E	6·5	0·2	45·5	+203	1·225	24,500
F	9·5	0·15	44·7	+202	0·985	19,700

The bulk of the ash (sodium sulphate) is contained in the small first fraction and if this fraction is excluded it is seen that the yield of purified methylated product is 35 g. from 45 g. of starch.

Methanolysis of the Combined Fractions.—The fractions were combined as follows: B (4·96 g.), C (5·47 g.), D (6·76 g.), E (6·49 g.) and F (8·41 g.). The total weight of the mixture is thus 32·09 g. and its mean methoxyl content is 44·5%.

The methylated starch was boiled for 8 hours with dry methyl alcohol (1 l.) containing 1·6% of hydrogen chloride. The clear solution was neutralised with lead carbonate, and the solution evaporated to dryness in the presence of a little lead carbonate. The dry residue was extracted with chloroform, the extract dried, and the solvent evaporated. The mixture of methylglucosides so obtained weighed 39·45 g.

Fractional Distillation of the Products of Methanolysis.—The usual procedure was adopted of distillation and redistillation in a high vacuum from a Widmer flask with a vacuum-jacketed column. The following fractionation was ultimately attained:

Fraction	1	2	3	4	5	6	7
Weight, g.	0·104	0·078	0·113	0·827	0·301	1·70	4·28
$n_D^{20°}$	1·4428	1·4428	1·4433	1·4543	1·4560	1·4560	1·4562
OMe, %	—	60·2	—	52·2	—	53·3	—
Fraction	8	9	10	11	12	13	14
Weight, g.	0·91	13·82	9·66	0·84	1·14	0·474	0·405
$n_D^{20°}$	1·4562	1·4563	1·4572	1·4592	1·4601	1·4638	1·4740
OMe, %	—	—	—	—	—	49·1	43·4

The undistillable residue weighed 0·85 g.

Inspection of refractive indices and methoxyl values indicates that the whole of the tetramethyl αβ-methylglucoside ($n_D^{20°}$ 1·4428; OMe 62·0%) produced is present in fractions 1 to 6; that the main product is 2 : 3 : 6-trimethyl αβ-methylglucoside ($n_D^{20°}$ 1·4560; OMe 52·6%); and that a small proportion of dimethyl methylglucoside (OMe, 41·9%) is also present in the final fractions.

That the tetramethyl methylglucoside is a derivative of glucose is indicated by the observation that for fraction 3 ($[\alpha]_D^{15°}$ + 61·8°) the $n_D/[\alpha]_D$ ratio lies on the $n_D/[\alpha]_D$ curve for mixtures of the α- and the β-forms of tetramethyl methylglucopyranosides (cf. Hirst and Young, J., 1938, 1248). Furthermore, hydrolysis of fraction 3 with aqueous acid yielded crystalline tetramethyl αβ-glucopyranose of m. p. and mixed m. p. 79—84° and $[\alpha]_D^{16°}$ + 82·5° (*c*, 0·4 in water; equilibrium value).

The main product of hydrolysis of the methylated starch is 2 : 3 : 6-trimethyl glucose. Fractions 5 to 10 crystallised on keeping and from each was separated crystalline 2 : 3 : 6-trimethyl β-methylglucoside (m. p. and mixed m. p. 71°). The yield of the crystalline β-isomer from these fractions was 40%. Hydrolysis of the non-crystalline portion yielded crystalline 2 : 3 : 6-trimethyl glucose, m. p. and mixed m. p. 112—115°.

The proportion of end-group, tetramethyl methylglucoside, was assessed on the basis of the n_D values of fractions 1 to 6, the extreme values so calculated being 1·40 g. and 1·54 g. derived from 100 g. of methylated starch. These are corrected values (cf. Averill and Peat, J., 1938, 1244) and correspond to chain lengths of 88 and 80 glucose units respectively.

It must be pointed out that 1·5% represents the maximum amount of end-group that can be present and that therefore the average chain length of synthetic starch cannot be less than 80 glucose units. Thus, fraction 1 showed certain anomalies (*e.g.*, the $n_D/[\alpha]_D$ value did not conform to the curve for tetramethyl αβ-methylglucoside) which led to the suspicion that this fraction was not composed entirely of glucoside but contained an unknown proportion of methyl lævulate or other decomposition product. Nevertheless, in arriving at the value of 1·5%, it has been assumed that the whole of fraction 1 consists of tetramethyl αβ-methylglucoside. The proportion of end-group may therefore be somewhat less than 1·5%.

The amount of dimethyl methylglucoside is not great. The bulk of it is contained in fraction 14 and it is estimated that roughly 1·5 g./100 g. of methylated starch are present.

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15. *Studies on Seed Mucilages. Part II. The Seed Mucilage of* Plantago arenaria.

By W. A. G. NELSON and E. G. V. PERCIVAL.

P. arenaria seeds yielded an acid polysaccharide of equivalent weight *ca.* 2000 which gave on hydrolysis *d*-xylose (70%), *l*-arabinose (9·5%), *d*-galactose (3·3%), and an aldobionic acid (13%) composed of *d*-galacturonic acid and *d*-xylose.

Hydrolysis of the methylated mucilage gave trimethyl xylopyranose (*ca.* 30%), 2-methyl xylose (*ca.* 23%), tetramethyl galactopyranose (*ca.* 4%), and a mixture (*ca.* 40%) composed chiefly of 3 : 4-dimethyl xylose but probably containing methylated arabinoses in addition.

It is concluded that the polysaccharide contains xylopyranose and galactopyranose " end groups " in the ratio of 9 : 1, the remaining xylose residues being linked by 1 : 2-β-linkages or triply linked with a free hydroxyl group on C_3.

CONTINUING our studies on seed mucilages of the *Plantago* family (J., 1940, 1501), we have now completed a preliminary study of the composition of the mucilage of the so-called dark Psyllium seed used in pharmacy. All the commercial samples we obtained were identified as *Plantago arenaria*. Anderson and Fireman (*J. Biol. Chem.*, 1935, **109**, 437) investigated light Psyllium—presumably the seeds known as ispaghula (*P. ovata*)—but did not report the results of any methylation experiments.

The seed mucilage, which was superficially similar to that from *P. lanceolata* already described, contained about 5·4% of ash (as sulphate), which fell on prolonged dialysis to 3·3%. Direct titration gave an acid equivalent of *ca.* 2000; the pentosan content of the mucilage was 90%, and the uronic anhydride content 7·5%. Hydrolysis with oxalic acid produced a mixture of sugars (87%) containing *l*-arabinose (9·5%) and *d*-galactose (3%), the remainder being *d*-xylose, together with an aldobionic acid (12%) composed of *d*-xylose and *d*-galacturonic acid. There is thus a marked difference in the composition of this mucilage and that of *P. lanceolata* (Part I, *loc. cit.*), for in that case analysis showed pentosan 72%, methylpentosan 11%, and uronic anhydride 15%, and although a small proportion of *d*-galactose was present, no arabinose could be detected in the products of hydrolysis.

The arenaria mucilage gave an acetate and a methyl derivative having strong negative rotations, a

fact, coupled with a knowledge of the products of hydrolysis, indicating a predominance of β-links. The methylated derivative was hydrolysed and as complete a separation of the methylated glycosides as could be achieved by fractional distillation and anilide formation gave the following results: 29·5% of the methylated polysaccharide appeared as trimethyl xylopyranose, so this proportion must constitute xylopyranose " end groups " in the polysaccharide. From the weight of tetramethyl galactopyranose anilide isolated, 4·5% of tetramethyl galactopyranose is estimated to be present in the hydrolysis products, so it would seem that all the galactose in the mucilage is accounted for by galactopyranose end groups. 40·5% of the hydrolysate (from which the galactose had been removed) was chiefly a dimethyl xylose. Methylation yielded trimethyl xylopyranose in good yield, so substitution on C_5 in the xylose molecule was excluded, and repeated failures to isolate a crystalline dimethyl xylose anilide negatived 2 : 3-dimethyl xylose as a possibility. Oxidation yielded a δ-lactone which has not so far been obtained crystalline (cf. 3 : 4-dimethyl δ-xylonolactone; Part I, *loc. cit.*), although the corresponding amide gave a positive Weerman reaction and oxidation yielded an unsymmetrical hydroxydimethoxyglutaric acid. These facts make it necessary to conclude that this fraction is mainly 3 : 4-dimethyl xylose (cf. Part I), but the failure to obtain crystalline derivatives does not exclude the possibility that the arabinose fragment is also present. A small quantity of a crystalline anilide, m. p. 170°, could be isolated from this fraction after removal of the tetramethyl galactose anilide. Analysis revealed that this was a dimethyl pentose anilide. The same substance was isolated from the hydrolysis products of the methylated mucilage of *Plantago ovata* and since this polysaccharide contains a higher proportion of arabinose than the polysaccharide under review, it is thought probable that this anilide is a dimethyl *l*-arabinose anilide. If so, it cannot be 2 : 3- or 2 : 4-dimethyl arabinose anilide (Smith, J., 1939, 744, 753) and 2 : 5-dimethyl arabinose does not appear to form an anilide (Smith, J., 1940, 1030), leaving 3 : 4- and 3 : 5-dimethyl arabinose as possibilities. This point will be investigated further when a sufficient quantity of the anilide is available.

The remainder of the hydrolysis product (23%) appeared as crystalline 2-methyl xylose (Bywater, Haworth, Hirst, and Peat, J., 1937, 1983), of which the crystalline *anilide* is described.

By taking into account the equivalent of the mucilage and the proportion of galactose, an approximation may be made to the composition of the chemical unit. Such a unit may contain nine xylopyranose and one galactopyranose end groups, ten xylopyranose linking units (joined by 1 : 2-β-linkages) and three arabinose linking units, eight xylose residues with free hydroxyl groups on C_2 at branching points of the structure, and two galacturonic acid residues, which appear to form a more stable union with xylose than with galactose or arabinose. This unit containing thirty-three components would have a molecular weight of 4476, an equivalent weight of 2238 and would give 9% of galacturonic acid and 10% of arabinose on hydrolysis. The methyl derivative would yield trimethyl xylose 31·8%, tetramethyl galactose 4·3%, dimethyl pentoses 42·6%, and monomethyl xylose 24·2%. These values are similar to those found experimentally, but further work will be necessary before the ramifications of the molecule can be worked out.

Experimental.

Preparation of the Mucilage.—P. arenaria seeds (1 kg.) were steeped in water (12 l.) for 24 hours with occasional stirring. After filtration through muslin and washing with water (4 l.) the product was precipitated by alcohol (2 vols.) with stirring, dehydrated with successive small quantities of alcohol, washed with ether, and dried in a vacuum to give a fibrous product (50 g.) (Found: ash, 5·4% as sulphate, 3·3% after dialysis in running water for 7 days). When the mucilaginous solution prepared as above was poured into acidified alcohol (50 c.c. of concentrated hydrochloric acid/l.), the acid polysaccharide used in the subsequent operations was obtained (Found: equiv., by titration, 2000; uronic anhydride, 7·5%; pentosan, 89·8%; methyl pentosan, nil; ash, 0·6%).

Hydrolysis of the Mucilage with Oxalic Acid.—The mucilage (16·1 g.) in 3% oxalic acid (250 c.c.) was heated at 100° for 20 hours. The insoluble residue (0·13 g.) was removed; the resulting solution showed $[\alpha]_D^{16°}$ + 34°. Neutralisation with calcium carbonate, filtration, and concentration at 45°/15 mm. yielded a syrup (15·5 g.), which was dissolved in water (40 c.c.) and precipitated in alcohol to yield a calcium salt X (2·2 g.) and a syrup Y (13·2 g.).

X appeared to be the calcium salt of an aldobionic acid. It showed $[\alpha]_D^{18°}$ + 64° in water (*c*, 1·2) [Found: Ca, 5·7. Calc. for $(C_{11}H_{18}O_{11})_2Ca$: Ca, 5·8%].

Hydrolysis for 24 hours in an autoclave at 120° with sulphuric acid (4%), followed by neutralisation with barium carbonate, yielded a glass, $[\alpha]_D^{17°}$ + 24° in water (*c*, 0·5), from which extraction with alcohol yielded *d*-xylose, $[\alpha]_D^{17°}$ + 24° in water (*c*, 1·1), and a residue of barium salt, $[\alpha]_D^{17°}$ + 14° in water (*c*, 0·8), which yielded mucic acid, m. p. 220°, on oxidation with bromine water.

The syrup Y (1 g.) gave *l*-arabinosediphenylhydrazone (0·15 g.), m. p. 196°, unchanged on admixture with an authentic specimen. *l*-Arabinose gave a 71% yield of this product, so the arabinose content of the

syrup is calculated to be 9·5% or 8% of anhydroarabinose in the mucilage. Crystalline *d*-xylose (7·1 g.), m. p. 142° alone or when mixed with *d*-xylose, $[\alpha]_D^{17°}$ + 80° (initial), + 17·4° (after 4 hours; constant) in water (*c*, 0·7), was removed by treatment with acetic acid. A portion (2 g.) of the resulting syrup, from which further quantities of *d*-xylose subsequently crystallised, gave *d*-galactosephenylmethylhydrazone (0·28 g.), m. p. 187°, unchanged on admixture with an authentic specimen. This corresponds to 8·8% of *d*-galactose in Y or 3·3% in the mucilage, since galactose (1 g.) yields galactosephenylmethylhydrazone (1·55 g.).

Acetylation of the Mucilage.—The mucilage (10 g.) was moistened with alcohol and dispersed in pyridine (150 c.c.). Acetic anhydride (50 c.c.) was added, followed by a further 50 c.c. in small portions; the mixture was heated at 95° for 20 hours and pyridine (60 c.c.) and acetic anhydride (40 c.c.) were then added. After standing at room temperature for 2 days, the acetate was precipitated by pouring into water; the product (15 g.) was washed with water, alcohol, and ether. Repeated extraction with acetone–chloroform (1 : 1) gave a jelly-like mass (6·5 g.) (Found: CH_3·CO, 33·5%) and a soluble fraction, $[\alpha]_D^{17°}$ − 61° in chloroform (*c*, 0·7) (Found: CH_3·CO, 38·1%).

Methylation.—Both acetates on methylation yielded similar products, so the acetate was methylated directly in four operations, as described in Part I (*loc. cit.*), without extraction with solvents (OMe, 33·9%), $[\alpha]_D^{17°}$ − 100° in chloroform (*c*, 0·3), after the first and (OMe, 35·3%), $[\alpha]_D^{17°}$ − 104° in chloroform (*c*, 0·3) after three further methylations. Fractional precipitation from chloroform solution by light petroleum gave fractions almost identical, in methoxyl content and specific rotation, with the starting material.

Typical Hydrolysis of the Methylated Polysaccharide.—The methylated compound (10 g.) (OMe, 34·9%; $[\alpha]_D^{17°}$ − 104°) was boiled with methyl-alcoholic hydrogen chloride (200 c.c.; 3%) until the rotation became constant ($[\alpha]_D^{18°}$ + 54°). After neutralisation with silver carbonate and filtration the liquid was concentrated to yield a non-reducing syrup (10·9 g.), which was separated into four fractions by distillation. The first two were refractionated from a Claisen flask with a vacuum-jacketed column, giving finally:

	Yield, g.	B. p.	$n_D^{18°}$.
Fraction I	3·19	80—95°/0·02 mm. (bath temp.)	1·4400
,, II	3·80	95—115/0·02 mm. ,,	1·4563
,, III	1·84	115—130/0·02 mm. ,,	1·4660
,, IV	1·62	130—150/0·02 mm. ,,	1·4752

Fraction 1.—This had $[\alpha]_D^{16°}$ + 27° in chloroform (*c*, 0·6) (Found: OMe, 58·1. Calc. for $C_9H_{18}O_5$: OMe, 60·1%). A portion (2·1 g.) was hydrolysed at 100° for 2 hours with 2% nitric acid (25 c.c.), and the solution neutralised with barium carbonate and evaporated to dryness; the residue, repeatedly extracted with boiling acetone, gave a syrup (1·7 g.) which rapidly crystallised. The crystalline material (0·8 g.) had m. p. 89—90°, not depressed by authentic trimethyl xylopyranose, $[\alpha]_D^{19°}$ + 53° in water (*c*, 0·6), falling to + 20° (1 hour) (Found: C, 49·9; H, 8·5; OMe, 47·3. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·3; OMe, 48·4%).

The porous tile used for removing the crystals yielded, on extraction with acetone, a syrup (0·85 g.) which subsequently crystallised and had $n_D^{20°}$ 1·4561, $[\alpha]_D^{19°}$ + 4° in water (*c*, 0·6), rising to + 18°, and therefore contained trimethyl β-xylopyranose. No crystalline anilide could be obtained from this syrup.

Methylation of Fraction II.—Fraction II (0·8 g.), $[\alpha]_D^{15°}$ + 46° in chloroform (*c*, 0·7) (OMe, 47·4%), was thrice methylated with silver oxide and methyl iodide to give an oil (0·7 g.), $n_D^{19°}$ 1·4408, $[\alpha]_D^{16°}$ + 45° in water (*c*, 0·6) (Found: OMe, 58·3%); this (0·36 g.) was hydrolysed with 2% nitric acid to give a syrup (0·28 g.), which yielded crystals (0·2 g.), m. p. 89°, unchanged by authentic trimethyl xylopyranose.

Examination of the Hydrolysis Products of Fraction II.—Hydrolysis of fraction II (1·2 g.) as for fraction I yielded a reducing syrup (1·0 g.), $n_D^{18°}$ 1·4768, $[\alpha]_D^{17°}$ + 33° in water (*c*, 0·6) (Found: OMe, 34·8. Calc. for $C_7H_{14}O_5$: OMe, 34·8%).

Isolation and Removal of Tetramethyl Galactopyranose Anilide.—Hydrolysed fraction II (3·7 g.) was heated with aniline (1·9 g.) in alcohol (10 c.c.) for 1·5 hours and six crops of tetramethyl galactose anilide were separated (0·585 g.), m. p. 195°, not depressed by authentic material, $[\alpha]_D^{17°}$ − 73° in acetone (*c*, 0·6) (Found: C, 61·2; H, 8·0; OMe, 39·6. Calc. for $C_{16}H_{25}O_5N$: C, 61·7; H, 8·1; OMe, 39·9%). A seventh crop of crystals (0·05 g.) had m. p. 170°, $[\alpha]_D^{11°}$ − 74° in acetone (*c*, 0·4), (Found: C, 61·3; H, 7·7; N, 6·25; OMe, 23·2. $C_{13}H_{19}O_4N$ requires C, 61·6; H, 7·5; N, 5·5; OMe, 24·5%).

The quantity of this material was too small for further investigation, but it is thought likely to be a dimethyl arabinose anilide, a similar product having been obtained from *Plantago ovata* mucilage, which contains a higher proportion of *l*-arabinose than *P. arenaria*.

Tetramethyl Galactopyranose Anilide from P. lanceolata *Mucilage.*—Although not reported in Part I, hydrolysed fraction II of the hydrolysis products of *P. lanceolata* mucilage (0·3 g.) gave tetramethyl galactopyranose anilide (0·07 g.), m. p. 195°, unchanged on admixture with an authentic specimen.

Lactone Formation.—The remaining syrupy anilides were hydrolysed with sulphuric acid as described by Smith (J., 1939, 744) and the syrup obtained (1·5 g.) (Found: OMe, 33·2. Calc. for $C_7H_{14}O_5$: OMe, 34·8%) was oxidised with bromine in the usual way. The product obtained after neutralisation with silver carbonate, treatment with hydrogen sulphide, and extraction with ether, on distillation at 140°/0·05 mm. (0·8 g.) had $n_D^{16°}$ 1·4618, $[\alpha]_D^{16°}$ + 46° (5 mins. in water, *c*, 0·6); + 37° (1·6 hrs.); + 31° (3 hrs.); + 29° (4 hrs.; constant

value) (Found: OMe, 35·5. Calc. for $C_7H_{12}O_5$: OMe, 36·1%. 0·0484 G. required 5·1 c.c. of N/20-sodium hydroxide. Calc. for $C_7H_{12}O_5$: 5·5 c.c.).

The lactone yielded an amide, $[\alpha]_D^{17°}$ + 34° in water (*c*, 1·6) (Found: OMe, 30·2. Calc. for $C_7H_{15}O_5N$: OMe, 32·1%), 0·12 g. of which gave 0·03 g. of hydrazodicarbonamide, m. p. 257°, when subjected to the Weerman test.

Attempts to isolate crystalline 3 : 4-dimethyl β-methylxyloside and its *p*-toluenesulphonate (Robertson and Speedie, J., 1934, 824) were unsuccessful.

Oxidation with Nitric Acid.—The above lactone (0·5 g.) was oxidised, and the products esterified as described in Part I (*loc. cit.*). Distillation gave a syrup (0·3 g.), b. p. 130°/0·05 mm. (bath temp.), $n_D^{16°}$ 1·4460, $[\alpha]_D^{15°}$ + 45° in methyl alcohol (*c*, 0·7) (Found: OMe, 53·0. Calc. for $C_9H_{16}O_7$: OMe, 52·5%), which had identical properties with the hydroxydimethoxyglutaric ester described in Part I. Treatment with methyl-alcoholic ammonia yielded an amide, $[\alpha]_D$ + 25° in water (*c*, 0·5), 0·05 g. of which gave hydrazodicarbonamide (0·012 g.) when subjected to the Weerman test.

Fraction III.—Methylation and hydrolysis. Fraction III (0·5 g.), $[\alpha]_D^{17°}$ + 56° in chloroform (*c*, 0·6) (Found: OMe, 41·8%), was methylated four times with the Purdie reagents to yield a mobile oil (0·45 g.), $n_D^{18°}$ 1·4404, which on hydrolysis yielded trimethyl xylopyranose (0·13 g.), m. p. 90°, not depressed on admixture with an authentic specimen, together with a syrup (0·17 g.), $[\alpha]_D^{18°}$ + 22·6° in water (*c*, 0·7), which later crystallised almost completely to yield trimethyl xylopyranose, m. p. 89°. Anilide formation with the above syrup gave tetramethyl galactopyranose anilide, m. p. 196° (1%). Fraction III is therefore a 1 : 1 mixture of dimethyl and monomethyl methylxylosides containing a small amount of methylated galactosides. Hydrolysis (3·15 g.) in the usual way gave a syrup (2·94 g.) (OMe, 27·0%), which was treated with aniline (1·61 g.) in alcohol (7 c.c.). Three crops of crystals were obtained. Crop 1 (0·87 g.) on recrystallisation from ethyl acetate and light petroleum had m. p. 140°, $[\alpha]_D^{17°}$ + 135° after 5 minutes in ethyl acetate [(10 c.c.) and acetic acid (0·4 c.c.) (*c*, 0·7)]; +113° (10 mins.); + 97° (20 mins.); + 93° (30 mins.); + 82·6° (24 hrs., constant value); $[\alpha]_D^{16°}$ + 240° in ethyl acetate (*c*, 0·7) (cf. 2 : 3-dimethyl xylose anilide; Hampton, Haworth, and Hirst, J., 1929, 1739) (Found: C, 60·6; H, 7·2; N, 6·1; OMe, 13·3. $C_{12}H_{17}O_4N$ requires C, 60·3; H, 7·1; N, 5·9; OMe, 13·0%). Hydrolysis of the anilide as previously described gave quantitatively 2-methyl xylose, m. p. 132—134°, not depressed on admixture with an authentic specimen prepared by the method of Robertson and Speedie (*loc. cit.*) (Found: C, 44·4; H, 7·4. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·4%).

Crop 2 (0·04 g.) was tetramethyl galactopyranose anilide and crop 3 (0·07 g.) was a mixture of crops 1 and 2.

Hydrolysed fraction III was converted into the lactone, $[\alpha]_D^{17°}$ + 48° in water (*c*, 1·3) (initial); + 44° (3 hrs.; constant value), indicating the presence of some δ-lactone. The corresponding amide (0·1 g.) gave hydrazodicarbonamide (0·014 g.), m. p. 256°, on treatment according to Weerman.

Thus fraction III is composed of 2-methyl methylxylosides *ca.* 50% and tetramethyl methylgalactosides *ca.* 1%, the remainder being similar to fraction II.

Fraction IV. Isolation of 2-Methyl Xylose.—Fraction IV had $[\alpha]_D^{17°}$ + 75° in chloroform (*c*, 0·6) (Found: OMe, 33·2. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). Hydrolysis (2·54 g.) with 2% nitric acid gave a syrup, from which 2-methyl xylose (0·75 g.) crystallised, m. p. 134°, unchanged on admixture with authentic material, $[\alpha]_D^{18°}$ − 21° in water (*c*, 1·1) (initial); − 6° (5 mins.); + 19° (30 mins.); + 26·5° (90 mins.); + 36° (3 hrs. constant value) (Found: OMe, 18·2. Calc. for $C_6H_{12}O_5$: OMe, 18·9%).

0·1 G. yielded 0·03 g. of an osazone devoid of methoxyl, m. p. 160—161°, unchanged on admixture with *d*-xylosazone. The syrup (0·2 g.) from which the crystals had been removed also yielded *d*-xylosazone (0·06 g.). The syrupy residue crystallised almost completely to 2-methyl xylose on standing.

A search for the methylated uronic acid by ester determinations on the various fractions was unsuccessful. Fractions I, II, and III gave CO_2Me nil, fraction IV 1·2%, and the still residue 1%. It is concluded that decomposition had occurred during hydrolysis.

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16. *Reactions of Hydrazoic Acid. Part I.*

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Further applications of the Schmidt reaction have been investigated. Hydrazoic acid in the presence of concentrated sulphuric acid reacts smoothly with benzylideneacetone, methyl β-phenylethyl ketone, α-benzyl-α-methylacetone, and benzylmalonic acid to give cinnamomethylamide, aceto-β-phenylethylamide, aceto-β-phenyl*iso*propylamide, and phenylalanine respectively. The reactions with podocarpic acid, *o*-, *m*-, and *p*-toluic acids and stearic acid are also described. Esters such as methyl and ethyl benzoate react with the Schmidt reagent, forming aniline, and methyl azide decomposes similarly into hydrazoic acid in the presence of concentrated sulphuric acid, but ketones and acids are unaffected during the reaction.

A PUBLICATION of Adamson (J., 1939, 1564) on the preparation of amino-acids by an application of the Schmidt reaction with hydrazoic acid (*Acta Acad. Abœnsis math. phys.*, 1924, **2**, 38; *Ber.*, 1924, [*B*], **57**, 704; D.R.P. 1928, 500,435) has prompted us to record the results of our experiments with the same reagent, which are on somewhat similar lines.

A convenient method has been devised for the preparation of aceto-β-phenylethylamides, which are suitable intermediates for the preparation of *iso*quinoline derivatives by the Bischler–Napieralski method.

Benzylideneacetone reacts with hydrazoic acid and concentrated sulphuric acid to give cinnamomethylamide, which is resistant to hydrolysis:

$$CHPh{:}CH{\cdot}COMe \xrightarrow{N_3H/H_2SO_4} CHPh{:}CH{\cdot}CO{\cdot}NHMe$$

Methyl β-phenylethyl ketone, however, with the same reagent gives a good yield of aceto-β-phenylethylamide:

$$CH_2Ph{\cdot}CH_2{\cdot}COMe \xrightarrow{N_3H/H_2SO_4} CH_2Ph{\cdot}CH_2{\cdot}NH{\cdot}COMe.$$

That aceto-β-phenylethylamide was formed and not the isomeric β-phenylpropionomethylamide was proved by acid hydrolysis to β-phenylethylamine and conversion into 1-methyl-3 : 4-dihydro*iso*quinoline (Späth, Berger, and Kuntara, *Ber.*, 1930, **63**, 136).

Similarly, α-benzyl-α-methylacetone reacts with hydrazoic acid and sulphuric acid at 0° to give a good yield of aceto-β-phenyl*iso*propylamide. The constitution of the compound was proved by its conversion, by treatment with phosphoric oxide in boiling tetralin, into 1 : 3-dimethyl-3 : 4-dihydro*iso*quinoline, isolated as its picrate (cf. Hey, J., 1930, 20). Hydrolysis of the acetyl derivative with hydrochloric acid gave *dl*-β-phenyl*iso*propylamine, the inactive form of the physiologically active benzedrine.

In a further experiment to obtain compounds of physiological importance, benzylmalonic acid was treated with the Schmidt reagent in chloroform–dioxan solution at 40°, but the yield of *dl*-phenylalanine was only 16% (cf. a similar experiment with malonic acid by Adamson, *loc. cit.*).

Most of the acids so far studied in reaction with hydrazoic acid have been benzoic and related acids and aliphatic acids with the carboxyl group attached to a primary carbon atom. The action of hydrazoic acid on podocarpic acid, which apparently contains a carboxyl group attached to a tertiary carbon atom (Sherwood and Short, J., 1938, 1006), gives an amine in good yield, so there can be little steric effect in the Schmidt reaction.

The solvent as well as the catalyst in the Schmidt reaction has a marked effect on the yield. Schmidt records an 85% conversion of benzoic acid into aniline in chloroform solution. In benzene and anhydrous ether yields of 85·5% and 24% respectively have been obtained under similar conditions, and the use of 75% sulphuric acid reduces the yield to 15% in chloroform solution. In boiling chloroform the yield is decreased to 44%.

Esters as well as acids react with the Schmidt reagent, methyl and ethyl benzoate yielding 26% and 24% respectively of aniline in either benzene or chloroform.

In agreement with Oesterlin (*Angew. Chem.*, 1932, **45**, 536) we have found that the position of a substituent markedly influences the yield of the substituted aniline from the corresponding benzoic acid; *e.g.*, *o*-, *m*-, and *p*-toluic acids give yields of 46%, 24%, and 70% respectively of the corresponding toluidines with 50% excess of hydrazoic acid. A quantitative examination of a number of meta-substituted benzoic acids with this reagent has been completed, the results of which will be communicated shortly.

Schmidt (*loc. cit.*) suggests that hydrazoic acid reacts through the imino-radical. On this basis methyl azide might similarly give rise to the $CH_3{\cdot}N{:}$ radical on decomposition, capable of reacting with ketones and acids to yield methylamides and secondary methylamines respectively. Although methyl azide decomposes similarly to hydrazoic acid, ketones and acids are unaffected during the reaction.

EXPERIMENTAL.

Action of Hydrazoic Acid on Benzylideneacetone.—Benzylideneacetone (5 g.; 1 mol.), dissolved in chloroform (75 c.c.), was mixed with a chloroform solution of hydrazoic acid (33 c.c. of 5·6% solution; 1¼ mols.) and cooled in ice–salt. Concentrated sulphuric acid (10 c.c.) was then added dropwise with stirring. After the rapid evolution of gas had ceased, the mixture was heated at 60° for 45 minutes. After cooling, the sulphuric acid layer was poured into water (250 c.c.), yielding a heavy brown oil, which solidified, m. p. 110° after recrystallisation from water. A further amount was obtained when the acid filtrate was made alkaline with ammonia. The crystals had the same m. p. 111° and physical properties as cinnamomethylamide (Orton, J., 1901, **79**, 1355; Vorländer, *Annalen*, 1902, **320**, 881).

Action of Hydrazoic Acid on Methyl β-Phenylethyl Ketone.—The ketone was prepared by catalytic hydrogenation of benzylideneacetone (Smith, J., 1914, **105**, 1706) and had b. p. 111—112°/10 mm., $n_D^{25°}$ 1·5140. The *dinitrophenylhydrazone* formed scarlet plates from alcohol, m. p. 131—132° (Found: N, 17·2. $C_{16}H_{16}O_4N_4$

requires N, 17·1%). To a rapidly stirred mixture of the ketone (20 g.; 1 mol.) in chloroform (10 c.c.) and concentrated sulphuric acid (36 c.c.) at 0°, a chloroform solution of hydrazoic acid (110 c.c. of 5·4% solution; 1 mol.) was added during 1 hour. After a further 45 minutes' stirring, the acid layer was poured into water (400 c.c.); it yielded to ether an oil, b. p. 126—127°/*ca.* 0·1 mm. (yield, 62·5%). Although the oil crystallised spontaneously on cooling (m. p. 42°), in agreement with other workers (Bischler and Napieralski, *Ber.*, 1893, **26**, 1905; Michaelis and Linow, *ibid.*, p. 2167; Decker, *Annalen*, 1913, **395**, 287), it could not be recrystallised from normal solvents. The constitution, however, was proved by hydrolysis with boiling concentrated hydrochloric acid to β-phenylethylamine, obtained as a viscous oil which formed a picrate, m. p. 170—171°, an oxalate, m. p. 180—180·5°, and a benzoyl derivative, m. p. 114—115° (the corresponding derivatives of β-phenylethylamine have m. p. 170—174°, 181°, and 114° respectively). Confirmation was obtained by conversion into 1-methyl-3 : 4-dihydro*iso*quinoline by heating with phosphoric oxide in boiling tetralin (Späth, Berger, and Kuntara, *loc. cit.*)—the picrate separated from methyl alcohol in long needles, m. p. 192° (Späth *et al.* record m. p. 188—190°).

Action of Hydrazoic Acid on α-Benzyl-α-methylacetone.—α-Benzylidene-α-methylacetone, b. p. 132—133°/12 mm. (Bogert and Davidson, *J. Amer. Chem. Soc.*, 1932, **54**, 334) was hydrogenated under pressure (45 lb.) in glacial acetic acid solution in the presence of palladium-charcoal to give α-benzyl-α-methylacetone, b. p. 111°/10 mm. The *dinitrophenylhydrazone* crystallised from alcohol in yellow plates, m. p. 81° (Found: N, 16·5. $C_{17}H_{18}O_4N_4$ requires N, 16·4%).

A solution of hydrazoic acid in chloroform (105 c.c. of 5·25%; 1 mol.) was slowly added with stirring to a solution of α-benzyl-α-methylacetone (20 g.) in chloroform (10 c.c.) in presence of concentrated sulphuric acid (35 c.c.) at 0°. Brisk evolution of gas occurred and was complete in 2½ hours. The acid layer, when worked up in the usual way, gave an oil, b. p. 135—136°/0·1—0·2 mm., solidifying on standing to crystals, m. p. 63° (yield, 48%). Crystallisation from light petroleum yielded pure aceto-β-phenyl*iso*proylamide, m. p. 67° (Hey, *loc. cit.*, records m. p. 64°). The constitution was proved as in the previous case by acid hydrolysis to β-phenyl*iso*propylamine, which formed a picrate, m. p. 142·5—143° (lit., m. p. 143°), and conversion into 1 : 3-dimethyl-3 : 4-dihydro*iso*quinoline, isolated as the picrate, m. p. 135·5° (Hey records m. p. 136°).

Action of Hydrazoic Acid on Benzylmalonic Acid.—To a solution of benzylmalonic acid (6·5 g.; 1 mol.) in a mixture of chloroform (40 c.c.) and dioxan (5 c.c.) were added 40 c.c. of a 5% solution of hydrazoic acid in chloroform, followed dropwise by concentrated sulphuric acid (15 c.c.). The mixture was rapidly stirred for 2 hours at 40°, but the evolution of nitrogen was not brisk. The acid layer was poured into water (100 c.c.) containing crystalline sodium acetate (77 g.). On concentration *dl*-phenylalanine was obtained mixed with sodium sulphate. After crystallisation from hot water it had m. p. 256—257° (decomp.) (yield, 16%); the benzoyl derivative had m. p. 185—186° (lit., m. p. 186—187°).

Action of Hydrazoic Acid on Podocarpic Acid.—To a mixture of podocarpic acid (10 g.) in chloroform (80 c.c.) and hydrazoic acid in the same solvent (39 c.c. of 5% solution; 1½ mols.) at 40°, concentrated sulphuric acid (10·5 c.c.) was added with stirring during 3 hours. The dark blue sulphuric acid layer was poured into water, yielding a white solid. The *sulphate* of the base so formed crystallised from dilute sulphuric acid in colourless plates, m. p. 279° (decomp.) (Found: C, 55·8; H, 7·4. $C_{16}H_{23}ON,H_2SO_4$ requires C, 55·9; H, 7·3%). The amine did not couple with β-naphthol after treatment with nitrous acid.

Action of Hydrazoic Acid on Methyl and Ethyl Benzoate.—Ethyl benzoate (5 g.) in chloroform solution (50 c.c.), when treated under the usual conditions with hydrazoic acid (1·5 mols.) at 40—45°, with concentrated sulphuric acid as catalyst, yielded 0·72 g. (23%) of aniline; from the chloroform layer, 3·5 g. (72%) of the ester were recovered by vacuum distillation. With 3 g. of the ester in benzene solution and similar treatment, 24% of aniline was obtained.

Similarly, methyl benzoate (5 g.) in chloroform (50 c.c.) yielded 0·92 g. (26%) of aniline, 3·5 g. (70%) of the ester being recovered.

Action of Hydrazoic Acid on o-, m-, *and* p-*Toluic Acids.*—The acids (5 g.), each dissolved in chloroform (40 c.c.), were allowed to react with hydrazoic acid in chloroform solution (1½ mols. of 4% solution) at 40—45° in the presence of concentrated sulphuric acid (13 c.c.). The products were worked up in the usual way, and the amines distilled in a vacuum and identified as their benzoyl derivatives. From the chloroform solutions the unchanged acids were obtained and purified. Yields of 46%, 70%, and 24% of the corresponding amines were obtained from *o*-, *m*-, and *p*-toluic acids respectively and 52%, 28%, and 74% of the original acids were recovered. A duplicate experiment with *p*-toluic acid gave almost identical results.

Action of Hydrazoic Acid on Stearic Acid.—15 G. of purified stearic acid, m. p. 69·5°, were dissolved in benzene (500 c.c.), concentrated sulphuric acid (30 c.c.) added, and the mixture stirred vigorously at 40°. Hydrazoic acid (52 c.c. of a 5·3% solution in benzene; 1·2 mols.) was then added slowly. After the reaction had ceased (2 hrs.) the acid layer was poured into water, precipitating the sulphate of heptadecylamine, which crystallised from alcohol in plates turning brown at 195° and decomposing at 200° (yield, 96%). The benzoyl derivative obtained therefrom had m. p. 81°, that recorded by von Braun and Sobecki (*Ber.*, 1911, **44**, 1473).

We are indebted to the Chemical Society for a grant.

Auckland University College, Auckland, New Zealand. [*Received, March 24th*, 1941.]

OBITUARY NOTICES.

ROBERT JOHN FLINTOFF.

1873—1941.

ROBERT JOHN FLINTOFF, the eldest son of Frances Egerton Flintoff, was born at Manchester on August 15th, 1873. He received his education at the Manchester Grammar School, and at Owen's College. On leaving college he carried on the business of a calico printer (Messrs. Fred Scott and Co., Ltd.), and on retirement in May, 1908, lived for a time at Haxby, near York, afterwards at Bridlington, and for the last 16 years of his life at Water Ark Lodge, Goathland.

He was one of the best known figures in North Country natural history circles, and was looked upon as an authority on the natural history of the fauna and flora of the district in which he lived. He was the author of many contributions to the *North Western Naturalist* and to other journals. As founder in 1936 of the Northern Ecological Society, he harnessed a remarkable team of scientific workers to study the life-forms as conditioned by native environment. He took a particular pride in his own beautiful garden at Water Ark Lodge, where visitors were always welcome.

When a young man he took a keen interest in rowing and for many years was captain of Hollingworth Lake Rowing Club. As a man, he was cheerful and forthright; a stickler for accuracy in scientific matters, and though not suffering fools gladly, his disarming smile and deep sincerity banished any feeling of resentment that one less endowed might have aroused. Though not a Quaker himself, he was proud of his Quaker ancestry. His great grandfather, Joseph Flintoff, who became Chairman of the Manchester Royal Exchange in 1823, and with another Quaker assisted in founding the firm of Jacob Bright and Co., lies in the old Quaker burial ground of Bishophill, York. As a friend, Flintoff's loyalty was complete, transcending the barriers of race, creed or class, and he could number among his intimates not only men of high intellectual ability but simple-hearted village craftsmen.

He was a Fellow of the Linnean Society, and was elected a Fellow of The Chemical Society in June, 1894.

His death took place suddenly at his residence in Goathland on September 13th, 1941. He was a bachelor, and leaves one brother, Mr. Thomas Flintoff, and many friends to mourn the loss of one who was devoted to the widening and dissemination of human knowledge, and who ever cultivated the joys of true friendship.

T. FLINTOFF.

MR. WILLIAM MACNAB, C.B.E.*

BY the death of Mr. William Macnab, on September 2nd, at the ripe age of eighty-four, we have to record the loss of one who not only made original contributions to our knowledge of explosives, both as to their properties and manufacture, but who in addition must be considered as a pioneer in the recognition of the importance of chemical engineering in Great Britain.

Coming from Greenock, his father being a ship-builder there, he took up the subject of sugar chemistry, after a training at the University of Glasgow, where he made a life-long friendship with Ramsay. Fond of travelling, he spent some time in Germany in connexion with sugar and later in Canada and the United States; in Siberia also he passed an adventurous two years engaged in prospecting. He could converse readily in French, German, and Russian.

About the age of thirty Macnab took up a consulting practice in partnership with C. Napier Hake and carried this on after his partner had left for Australia to become Inspector of Explosives for Victoria. It was at this period and in collaboration with Napier Hake that he undertook the translation and collation of Berthelot's papers on explosives, publishing in 1892 " Explosives and their Power," which is a handbook constantly referred to by all explosives chemists. This book describes the application of thermochemistry to explosives, gives Berthelot's calorimetric data for explosive reactions over a wide field and deals with many explosive phenomena.

At this time Macnab began his original contributions to the study of explosives, and with E. Ristori published researches on partially gelatinized and on fully gelatinized propellants (*Proc. Roy. Soc.*, **56**, 8; 1894). A bomb of the Berthelot type was used; heat values and volumes of gases given off with their composition were measured, together with the metamorphosis undergone by gelatinized mixtures of nitroglycerine with various nitrocelluloses when exploded in the bomb. This work had importance as well as

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accuracy, as was shown by the agreement of products with original composition of explosive. Pressures were measured in another bomb and these agreed with the values found by Sir A. Noble. Later (*Proc. Roy. Soc.*, **66**, 221; 1900) the same authors described attempts to determine the temperature of explosion (apart from its calculation from heat values and specific heats) by a method depending on the use of thermocouples of gradually decreasing diameter, the deflexion of a galvanometer mirror being photographically recorded. Although absolute values for temperature were not obtained, the results placed different explosive mixtures in a comparative sequence. This subject was continued in collaboration with A. E. Leighton (*J. Soc. Chem. Ind.*, **23**, 298; 1904) when the heat values were compared with the galvanometer throws, the order of the powders being broadly the same in both cases.

Always interested in chemical manufacture, Macnab played an important part during the War of 1914—18, when he became a technical adviser on Lord Moulton's staff, where full use was made of his experience in the manufacture, as well as knowledge of the properties, of explosives. Working in close conjunction with Kenneth B. Quinan he was intimately associated with the design of factories for high explosives and propellants, as well as with their administration when erected. Impressed by Quinan's method of holding monthly meetings of his factory staffs at which costs and efficiencies were minutely discussed, resulting in notable improvements in technique, Macnab undertook after the War the compilation of an important series entitled " Technical Records of Explosives Supply, 1915—1918 " (H.M. Stationery Office), dealing with intermediates and finished explosives. These are valuable studies in which the chemical engineering aspect is emphasised, and serve as text-books for any school in that subject, for they include not only the theory of the processes, but also sketches of designs of plants, instructions for running them, calculations of heat-transfer and loss, and choice of materials of construction. They are so framed as to assist a student engaged in general chemical engineering problems, not necessarily those dealing with explosives.

This methodical approach appealed to Macnab, who lectured on the subject at University College, London, and led to his support in starting the Department of Chemical Engineering there. This movement was strongly urged by Quinan also who had felt the grievous lack of chemical engineers during the War of 1914—18. Some chemical achievements during this time were described by Macnab in his Hurter Memorial Lecture in 1922. For the same reason he acted as one of the founders of the Institution of Chemical Engineers, becoming its president in 1934, the William Macnab Medal of that Institution commemorating his name. Much of the success of the Seventh International Congress of Applied Chemistry in 1909 was due to him. For his work in the War he was made a C.B.E. in 1920.

Of striking appearance, suggesting robust health, with rosy cheeks and pointed beard, always dressed with perfect neatness, he will be remembered for his geniality and unselfish kindliness; and his friends will remember the hospitality of his charming wife and himself at his house on the river, where it was his custom to entertain them, take them out in one of his craft, for he was a master sailor, and to some of them show his experiments in calorimetry with a large bomb that needed his athletic frame to manhandle. In his London house also, his skill at the piano and liking for good music will be remembered by many.

ROBERT ROBERTSON.

HERMANN GÜNTHER GOTTSCHALT MOHRHENN.

1909—1941.

THE death of Dr. Mohrhenn in a road accident at the early age of 32 is a serious loss to our Society. On the evening of July 3rd he was cycling to his home in Crouch End when he was struck from his bicycle and killed by a trailer drawn by a heavy lorry.

About half his short scientific life was spent at University College, London, and half at the British Launderers' Research Association. He was a man who made friends particularly easily, and in both these institutions, as well as the social and religious circle in which he moved, his loss will be severely felt by many whose esteem and affection he commanded.

Mohrhenn received his general education at Tollington School, Muswell Hill, and then proceeded to University College, where he graduated with Second Class Honours in Chemistry in 1930. He remained at College as a research student and worker for a further five years, obtaining his Ph.D. degree during this period. In 1935 he joined the staff of the British Launderers' Research Association. Here he was concerned for several years with problems connected with wool washing. Shortly before his death he had taken sole charge of applied research in the experimental laundry of the Association.

The work carried out by Mohrhenn in the chemical laboratories of University College is described

in two papers of the Journal of the Chemical Society (J., 1935, 949, 1482). They represent a development of Bjerrum's well-known method of measuring the molecular dimensions of a dibasic acid by the determination of its first and second dissociation constants. The original crude theory had been to some extent refined, and in 1930 it seemed that further advance along those lines would be very difficult (although substantial new improvements of the theory have since been secured by Kirkwood and Westheimer). Mohrhenn therefore set out to check, and empirically correct, the method by applying it to a number of isomeric and stereoisomeric acids of the *cyclo*pentane series, believed to have a rigid structure and known dimensions. In the second paper he applies a corresponding method to the parallel theory which connects the molecular dimensions of dicarboxylic esters with the rate constants for the first and second stages of their saponification.

Mohrhenn had a most acute scientific conscience and a high sense of responsibility—his personal responsibility to posterity, for the accuracy of his work. Neither care nor patience was spared in carrying purifications to the limit, and in squeezing the last possible drop of precision out of the physical methods employed. Twice he insisted on discarding the results of nearly two years' labour because of small imperfections which could be corrected by repetition. His published work is a memorial to his sincerity and devotion.

Most people who are hard on themselves feel they have a right to exact high standards from others; but this was not Mohrhenn's way. Severe with himself, he was singularly gentle with others. His gift of sympathy and willingness to help others without counting time and trouble brought him many friends whom he kept for life. He was closely identified with the social and religious life of Park Chapel, and was associated with its Youth Fellowship and with the Hornsey Christian Youth Council.

At the time of his death he was living with his mother and sister at " Sonningholme," Clifton Rd., Crouch End, N.8.

C. K. INGOLD.

WILLIAM REGINALD ORMANDY.

1870—1941.

To those who had the honour of personal friendship the loss of Ormandy leaves a gap impossible to fill and a loss that is irreparable, for he was not only a man of science with many facets of interest but also a very human and kindly personality. He was born in 1870, and educated at Wigan Grammar School and at Owen's College, Manchester, where he graduated, becoming Bishop Berkeley Fellow in 1890. He took his Doctorate in 1894 after three years' work at Tübingen. For four years he taught at the Crewkerne Grammar School and at the Technical School, St. Helens. These four years probably helped to formalise Ormandy's mind—he always remained a teacher, informative in matter and impressive in diction, with a wide range of reading and knowledge and no little share of wisdom.

He had an astonishingly wide range of professional interests. He was research chemist to Messrs. Pilkington Ltd., to the St. Helens Cable and Rubber Works, to Joseph Crosfield's of Warrington, and eventually head of a well-known firm of Consultants in Manchester and London.

Being a man who believed his fellow-creatures to be as interesting as chemical entities, he rapidly found scope for his abundant energy in a multiplicity of societies. He served on the Council of the Institute of Petroleum for many years, on the Council of the Institution of Chemical Engineers, of the Institute of Metals and of the Ceramic Society. He was a Past President of the Institute of Automobile Engineers, and Chairman of the Chemical Engineering Group of the Society of Chemical Industry.

He was specially interested in liquid and gaseous fuels, and perhaps it is not generally known that he was intimately concerned with the earliest work on hydrogenation of coal and oil carried out by Bergius. In point of fact he pioneered the development of this subject in Great Britain.

In no less degree was he active in insisting on the value of alcohol as a component of motor spirit, and indeed was Consultant to the Distillers' Company for many years.

One of his outstanding researches was concerned with the action of sulphuric acid on olefins. In this work he showed that a saturated hydrocarbon was produced. This statement brought about a storm of controversy but subsequent investigation showed that Ormandy was right. Is it too much to say that here he was the lineal ancestor of modern processes of hydro-polymerisation?

But reverting to Ormandy the man, those who knew him best carry pleasant memories of an outstanding personality, a controversialist brilliant in speech and repartee, kindly and tolerant in his dealings with his associates, a man of great knowledge but not deficient in understanding.

A. E. DUNSTAN.

ROBERT ROBISON.

1883—1941.

ROBERT ROBISON died suddenly on June 18th, 1941. By his passing at the early age of 57 the Society has lost a distinguished Fellow.

Robison was born at Newark-on-Trent in 1883 and obtained his early education at the Magnus Grammar School in his native town. He entered University College, Nottingham, in 1900, attended the usual course of study for an honours degree in chemistry, and graduated B.Sc. in 1906. He commenced research, under the direction of Professor F. S. Kipping, some time before he obtained his degree and after a year's further research he was awarded an " 1851 Exhibition " scholarship for his work on the benzyl and benzylethyl derivatives of silicone (Robison and Kipping, J., 1908, **93**, 439). The next two years were spent in the laboratory of Professor Hantzsch at Leipzig, where Robison carried out investigations bearing on the relationship between the colour and constitution of organic compounds. The result of these researches were embodied in two papers (Hantzsch and Robison, *Ber.*, 1910, **43**, 45, 92) and the degree of Ph.D. (*summa cum laude*) was awarded to him for his thesis entitled " Über die polychromen Salze aus Dimethyl und Diphenyl-Violursäure."

Robison returned to England in the summer of 1909 and a few months later was appointed lecturer and demonstrator in chemistry at University College, Galway, where work was started on possible methods for the synthesis of acridines, in collaboration with the late Professor Senier. The investigation remained unfinished, however, as in October, 1910, he was appointed to the post of lecturer and demonstrator in chemistry at University College, Nottingham. The problem of organic compounds of silicon was again resumed in collaboration with Professor Kipping, and during the next three years he investigated the preparation and properties of some silicanediols of the type $SiHR(OH)_2$ and certain condensation products of diphenylsilicanediol (Robison and Kipping, J., 1912, **101**, 2142, 2156; 1914, **105**, 40, 984). It seemed at this stage in his career that Robison was destined to occupy a Chair of Organic Chemistry. In February, 1913, however, he applied for the post of Assistant in the Biochemical Department of the Lister Institute of Preventive Medicine, and was appointed a Member of the Institute Staff the following month. Here for the first time Robison came in contact with biochemical problems. He commenced work with characteristic thoroughness and enthusiasm and, in collaboration with his new chief, Profession Harden, was soon able to announce, in a preliminary note (Harden and Robison, Proc., 1914, **30**, 16) the discovery of a new hexosephosphoric ester, which, although not at that time obtained in a pure condition, was identified as a hexosemonophosphoric ester. This ester, or more correctly, mixture of esters, was later known as the " Robison ester " and was destined to play an all-important part in the post-war development of biochemistry.

The War caused a complete break in Robison's work which lasted for the years 1914—1918. In December, 1914, he enlisted in the Sanitary Section of the Royal Army Medical Corps and after a short period of training at home was placed in charge of a sanitary unit and left for Egypt with the 29th Division early in 1915. Soon after his arrival at Alexandria he became ill with dysentery; although still far from well, he proceeded a few weeks later to Mudros, where he was stationed during the whole of the campaign in Gallipoli. During this period his general health suffered considerably, but on his return to Egypt he spent some months doing general hygiene work at El Kantara before giving up and going into hospital at Alexandria. He was finally invalided home early in 1917. With his return to health later in the same year Robison was posted with the rank of captain to a hygiene unit laboratory attached to the Italian Expeditionary Force; he remained in Italy until some months after the armistice in 1918.

After his return to the Lister Institute, Robison at first collaborated with Harden in a number of investigations concerned with the antiscorbutic properties of concentrated fruit juices and the nature of the sulphuric acid test for liver oils. Subsequently he worked on the biological value of proteins in milk, wheat, and gelatin and availed himself of this opportunity to study the distribution of the nitrogenous constituents of the urine on a diet containing a minimal amount of nitrogen. During these investigations Robison became his own experimental animal and as a result of the severe strain thrown on his digestive machinery he was forced to go into hospital for repair. On restoration to reasonable health he reverted to an investigation on the hexosemonophosphoric ester he had previously described with Harden in 1914. The isolation and purification of the ester proved to be a difficult problem, but Robison finally published an account of this important work (*Biochem. J.*, 1922, **16**, 809). His thoroughness caused him to investigate in extreme detail the products of a particular reaction and for many years he was busy separating and identifying the phosphoric esters produced during alcoholic fermentation. The care and skill with which his work was undertaken can be judged from the fact that six new hexose-

phosphoric esters were discovered. In a series of papers in collaboration with numerous co-workers he was thus able to record the isolation and identification of trehalosemonophosphoric ester (Robison and Morgan, *Biochem. J.*, 1928, **22**, 1277), glucose 6-phosphate (Robison and King, *ibid.*, 1931, **25**, 323), mannose 6-phosphate (Robison, *ibid.*, 1932, **26**, 219; Robison and Jephcott, *ibid.*, 1934, **28**, 1844), fructose 6-phosphate (Macleod and Robison, *ibid.*, 1933, **27**, 286), fructose 1-phosphate (Tankó and Robison, *ibid.*, 1935, **29**, 961), and an unidentified ester (Robison, Macfarlane, and Tazelaar, *Nature*, 1938, **142**, 114), the sugar component of which resembles in many ways mannoketoheptose, a 7-carbon atom sugar that was isolated from the avocado pear by La Forge. A close examination of these papers shows the tenacity and resolution with which Robison carried out his investigations and up to the time of his death he was still actively engaged on the isolation of certain unidentified sugar phosphoric esters.

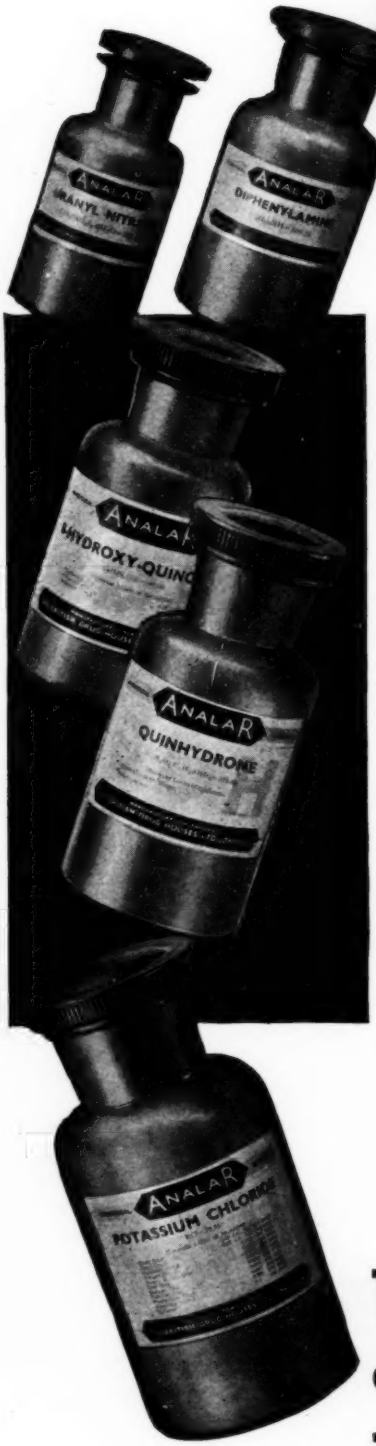
Early in 1923 Robison discovered the enzyme, phosphatase, in the aqueous extracts of bones of young, rapidly growing animals and worked out a method for obtaining very active phosphatase preparations which could hydrolyse many different monosubstituted phosphoric esters but had only slight action on disubstituted esters such as diethyl phosphate, and little or no hydrolytic action on lecithin. Robison used the bone phosphatase as a biochemical reagent in several investigations, of which those dealing with the removal of the phosphoric acid groups from the methylated phosphoric esters of hexose di- and monophosphates (Morgan and Robison, *Biochem. J.*, 1928, **22**, 1270; King, McLaughlin, and Morgan, *ibid.*, 1931, **25**, 310), the isolation of crystalline trehalose from trehalose monophosphate (Robison and Morgan, *ibid.*, 1928, **22**, 1277), and the preparation of gluconic acid from the phosphogluconate obtained by the bromine oxidation of glucose monophosphate (Robison and King, *ibid.*, 1931, **25**, 323) are interesting examples and are sufficient to show the importance of this method of attack on the chemical constitution of the sugar phosphoric esters.

In some of his earlier experiments Robison observed that during the hydrolysis of fructose diphosphate (1 : 6-diphosphofructofuranose) by preparations of the bone phosphatase, a part of the sugars liberated, following the removal of the phosphoric acid groups, suffered an intramolecular change and gave rise to a mixture of aldose and ketose sugars (Martland and Robison, *ibid.*, 1929, **23**, 237), and similar results were also obtained with the glucose monophosphoric ester (Robison and King, *ibid.*, 1931, **25**, 323). A more detailed study of these changes was undertaken later (Macleod and Robison, *ibid.*, 1933, **27**, 286) and the investigation soon revealed that the proportion of aldose formed during the hydrolysis varied with the phosphatase preparation employed. In a later communication in collaboration with Tankó (*ibid.*, 1935, **29**, 901) he announced the discovery of the enzyme phosphohexosekinase, which he isolated from crude preparations of bone phosphatase and from bone marrow extracts. Robison finally showed that the phosphohexosekinase converts fructose 6-phosphate and glucose 6-phosphate into equilibrium mixtures of aldo- and keto-esters, and demonstrated that the enzyme had no action on fructose 1-phosphate or on fructose 1 : 6-diphosphate unless phosphatase was present and first removed the phosphate group from position 1.

Robison's more biological work involving contributions to our knowledge of the chemical mechanism underlying the formation of bone has been reviewed in detail elsewhere * and need be given here only in outline. Early in 1922 he observed that by the action of the enzyme emulsin on the soluble calcium salt of hexose monophosphoric acid, hydrolysis occurred and inorganic phosphate was precipitated from solution as insoluble calcium phosphate. This observation suggested to him that a similar mechanism might be concerned with the deposition of the calcium salts of bone. The next step was to obtain direct experimental evidence for the presence of phosphatase in cartilage that was about to calcify and this he did by placing the bones of young rats in solutions of calcium hexose monophosphate. In the course of a few hours a deposit of calcium phosphate was formed and thus his original idea seemed to be correct. Further experiments, carried out with the proper controls, soon confirmed the fact that ossifying cartilage does indeed contain a very active phosphatase. From this time on he slowly developed a theory of bone calcification and produced much valuable experimental evidence to support the view that the full calcifying mechanism consists of a complex enzyme system of which phosphatase is one component. According to this idea, which was first published in 1934, the bone may itself be able to synthesise phosphoric esters from inorganic phosphate, these esters being subsequently hydrolysed at the site of calcification. From this time on his conception of the mechanism underlying the general process of calcification has been generally accepted. The many papers written on this subject in collaboration with several co-workers is a record of Robison's greatest work and is a rare example of beautifully planned research carried out with outstanding skill.

Robison was elected a Fellow of the Royal Society in 1930 and was appointed, some months later,

* *Biochem. J.*, 1941, **35**.



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